

Emerging **M**arkets

Models of best practice for the
regulatory review of new medicines

Report of the CMR International Institute Workshop

5-6 December 2007, Geneva, Switzerland

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Institute for Regulatory Science



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CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

The CMR International Institute for Regulatory Science is a not-for-profit division of the Centre for Medicines Research International, Thomson Scientific. It works in the regulatory and policy arena and in close association with the research-based pharmaceutical industry and regulatory authorities around the world. The Institute operates autonomously with its own dedicated management and funding that is provided by income from a membership scheme.

The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

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Workshop Organisation

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Referenced information:

¹ Report of the CMR International Institute Workshop on The Emerging Markets: Regulatory issues and the impact on patients' Access to medicines, 2-3 March 2006, Geneva, Switzerland

² Report of the CMR International Institute Workshop on Global Drug Development: Asia's Role and contribution, 11-12 October 2006, Tokyo, Japan

Copies of these reports can be requested from the address given above (Distribution is normally restricted to member companies of the Institute and members of Regulatory Authorities).

CMR International Institute Workshop
THE EMERGING MARKETS:
MODELS OF BEST PRACTICE FOR THE REVIEW OF NEW MEDICINES
SECTION 1: OVERVIEW

Introduction

The CMR International Institute for Regulatory Science returned to Geneva for its second workshop on the regulation of new medicines in the Emerging Markets. A major objective was to identify best practices for the review of new medicines that make the most of limited resources and provide efficient and rapid access to new therapies whilst protecting patient safety.

The Workshop built on the discussions and recommendations from the first Emerging Market Workshop, March 2006¹ and also took account of related discussions from the Workshop held in October 2006 on the inclusion of Asian countries in Global Drug Development². Amongst a programme of speakers from senior positions in regulatory agencies and industry, the meeting also included collective *Round Table* discussions which made recommendations and observations on key issues

HIGHLIGHTS FROM THE ROUND TABLE DISCUSSIONS

Types of assessment and review models

Multiple scientific reviews: It is not a good use of limited agency resources for numerous different authorities to re-review the core ('safety, quality and efficacy') scientific evidence for a new drug substance. Better to utilise and 'recognise' the basic scientific reviews by reference agencies and focus local resources on benefit-risk assessment, quality issues, pharmacovigilance and labelling for the local market.

Benefit-Risk assessment criteria: Some degree of harmonisation should be feasible at a regional level but this is not a realistic *international* goal for the foreseeable future because of the degree to which such assessments are subjective and influenced by cultural and historical differences.

A single 'ideal' review model, for the sequence in which the different steps in a review are carried out, is not a current priority. The focus should be on improving the efficiency of established systems.

Evidence of authorisation by other agencies

The CPP (Certificate of a Pharmaceutical Product) is an important element in some markets but, in its current form, it remains an impediment to the global roll-out of new medicines. Radical changes to the format and scope are needed.

These include:

- Acceptance of an **electronic CPP** and less reliance on original paper documentation in order to reflect the current technological environment;

- **A separation** of its role as a GMP certificate and as evidence of authorisation in the issuing country to keep abreast of current trends towards multiple interchangeable manufacturing sites for globally marketed medicines

There should be greater flexibility in the acceptance of **alternatives to the CPP** as evidence of the regulatory status of new medicines, in particular, **information on reference agency websites**.

Exchange of Scientific Assessment Reports

Agencies in the Emerging Markets can benefit from the **assessment reports of reference agencies** by entering into confidentiality agreements. Industry is willing to cooperate with such schemes provided commercially sensitive information is adequately protected.

Regional schemes for the exchange of assessment reports between agencies (e.g., ASEAN members) would be a valuable step towards building mutual confidence among similar authorities and increasing harmonisation.

Assessment templates: It was recommended that the CMR International Institute should undertake a study of agency templates used for the assessment of clinical data although it would be premature and over-ambitious to consider a project for international harmonisation, at this stage.

Building Quality into the Review Process

'Fit for Purpose' quality standards: All agencies can improve the quality of their working practices but the standards should be realistic and not set so high that they impede efficiency.

Building **transparency** into the review process drives improvements in the system to the ultimate benefit of the public and patient.

Feedback: It was recommended that all agencies should introduce mechanisms, no matter how rudimentary, for exchanging views and feedback with companies after the assessment of a major application

Project Management is fundamental to improving and monitoring the quality of the review process, and should preferably include a single point of contact for companies after submitting an application and a mechanism to try to resolve differences of opinion during the review process.

Application tracking systems: It was recommended that agencies with the facilities to monitor timelines and provide feedback should publish summaries of their findings and share these with industry and other interested observers as part of the learning process.

^{1,2} See inside front cover for references

SYNOPSIS OF THE PROGRAMME

Session 1, chaired by **Professor Robert Peterson**, *University of British Columbia, Canada* looked at the benefits and limitations of current review process models and different types of scientific review.

Dr David Jefferys, *Vice President, Global Regulatory Affairs, Eisai R&D Company Ltd, UK* gave the introductory presentation that reviewed the current options for regulatory review of new medicines and for sharing assessment information among agencies.

Dr Neil McAuslane, *Director of the Institute for Regulatory Science*, presented some of the results from the Institute Study on the regulation and review of new medicines in the Emerging Markets, outlining the different review models and procedures that are currently being used.

Presentations followed on the procedures in individual countries which provided examples of different approaches and philosophies from recognition of reviews conducted elsewhere to building the capacity to carrying out full new drug reviews. The speakers were:

ARGENTINA: **Analía Pérez**, *Director of Drug Evaluation for ANMAT*

INDONESIA: **Lucky Slamet**, *Director of Therapeutic Products, Narcotics, Psychotropic, and Addictive Substance Control, NADFC*

INDIA: **Dr Eswara Reddy**, *Office of the Deputy Drugs Controller, CDSCO*

CHINA: **Dr Zili Li**, *Clinical Research Operations – Asia Pacific, MSD China Regulatory Policy Group*

SINGAPORE: **Dr Kian-Ming Lam**, *Deputy Director (Corporate Operations), CEO's Office, Health Sciences Authority, Singapore*

The second Session, chaired by **Colin Vickers**, *Head of Worldwide Regulatory Strategy, Pfizer Ltd*, considered ways to optimise resources by utilising the work carried out by other agencies.

Dr Herng-Der Chern, *Executive Director, Center for Drug Evaluation, Taiwan* described the 'risk-based' review system in Taiwan that combines recognising the review of other agencies with national assessment.

A panel of discussants took further the theme of the evidence needed in order to utilise the assessment of another agency:

MEXICO: **Patricia Pineda**, *Manager of International Affairs on Chemicals and Drugs, COFEPRIS*

INDUSTRY: **Ann Readman**, *Vice President International Regulatory Affairs, AstraZeneca UK Ltd*

WHO: **Dr Lembit Rägo**, *Coordinator Quality Assurance& Safety of Medicines, WHO, Geneva*

A quality review

Session 3 was chaired by **Dr Justina Molzon**, *Associate Director, International Programs, CDER, FDA, USA* and looked at 'best practices' for the review of new medicines, particularly the role of project management and related procedures to monitor the timeliness and integrity of the review process.

Professor Stuart Walker *Vice President and founder of the Institute* provided an overview the topic with a report of findings from the Institute's work with agencies in the Emerging Markets.

The importance of building quality into review procedures was then discussed by:

INDUSTRY: **Alistair Davidson**, *Vice President, International Regulatory Affairs, GlaxoSmithKline, UK*

AUSTRALIA: **Dr Jason Ferla**, *Drug Safety and Evaluation Branch, TGA, Australia*

MALAYSIA: **Noorizam Ibrahim**, *Head of New Chemical Entity Section, NPCB, Malaysia*

INDUSTRY: **Dr Matthias Hoepfner**, *VP, Head of GRA International, Bayer Healthcare AG, Germany*

Caroline Vanneste, *Project Manager, Good Review Practices, TPD, Health Canada* took up the theme of good project management with efficient, integrated tracking systems and this was discussed further by:

INDUSTRY: **Jennifer Chung** on behalf of **Mary Jane Nehring**, *Executive Director, Global Regulatory Affairs, Schering-Plough Corporation, USA*

WHO: **Mrs Precious Matsoso**, *Director, Department of Technical Cooperation for Essential Drugs and Traditional Medicines*

Clinical trial applications

Professor Stuart Walker chaired the final Session which reviewed the requirements for initiating clinical trials in the Emerging Markets and their integration into the global clinical development of new medicines.

Jennifer Collins, *Project Manager, CMR International Institute* presented findings from the Institute's study on clinical trial requirements in Emerging Markets.

Dr Paul Huckle, *Senior Vice President, US Regulatory Affairs, GlaxoSmithKline, USA* provided a presentation (given by Alistair Davidson) that looked at factors that influence companies in selecting countries for clinical trials.

Dr Jorge Samaha, *Coordinator, Clinical Trial Section, ANVISA* explained the way in clinical trial applications are handled in **Brazil** and further country perspectives for Taiwan and India were provided by previous speakers, **Dr Herng-Der Chern** and **Dr Eswara Reddy**.

The way forward

The Workshop concluded with a discussion, led by **Dr Neil McAuslane** and **Professor Stuart Walker** on topics for future study and discussion between the Institute, industry and regulatory agencies in the rapidly developing pharmaceutical markets of the world.

CMR International Institute Workshop

THE EMERGING MARKETS: MODELS OF BEST PRACTICE FOR THE REVIEW OF NEW MEDICINES

SECTION 2: OUTCOME

1. BACKGROUND TO THE WORKSHOP

Since 2004, the CMR International Institute for Regulatory Science has been working in association with the industry and agencies on an *Emerging Markets Programme* designed to develop a greater understanding of the regulatory aspirations, barriers and priorities that impact the review and availability of new medicines outside the ICH regions.

An Institute Workshop on the Emerging Markets¹ was held in March 2006 at which a number of recommendations were made including the need to define more clearly the regulatory models used by different agencies, the importance of setting realistic targets for review times and the benefits of establishing an open and transparent relationship between authorities and the industry.

These recommendations were built into the 2006/07 phase of the *Emerging Markets Programme* and reports from this study were an important element in the Programme for this Workshop. The discussions at the Workshop on requirements for initiating clinical trials in the Emerging Markets was also shaped by discussions at a previous Institute workshop on *Global Drug Development: Asia's Role and Contribution*².

2. SUMMARY OF THE WORKSHOP RECOMMENDATIONS

The Workshop programme included two 'Round Table' discussions at which the views of groups of participants were collected. The outcome of these discussions sessions are summarised below. The main conclusions are reproduced, as a two-page reference sheet in Annex 1 and background information on the discussion topics is given in Annex 2.

Round Table Discussion Session 1 (Topics A-C):

Moderator: **Colin Vickers**, Head, Worldwide Regulatory Strategy –International & Japan Liaison, Pfizer Ltd, UK

Chairpersons:	Rapporteurs:
Dr Supriya Sharma, Director General, Therapeutic Products Directorate, Health Canada	Dr David Jefferys, Vice President, Global Regulatory, Eisai R&D Management Co Ltd, UK
Dr Jason Ferla, Head, Clinical Evaluation Section 3 (Cardiovascular and Rheumatology), Therapeutic Goods Administration, Australia	Dr Susan Forda, Executive Director, International Regulatory Affairs (EU & Intercontinental), Eli Lilly and Company Ltd, UK
Dr Justina Molzon, Associate Director, International Programs, CDER, Food and Drug Administration, USA	Carole Chappell, Vice President, International Regulatory Affairs, Allergan, UK
Precious Matsoso, Director, Technical Cooperation for Essential Drugs and Traditional Medicines, WHO, Switzerland	Fraser Stodart, Regional Regulatory Director – Africa and Middle East – Worldwide Regulatory Strategy – International, Pfizer Ltd, USA
Professor Robert Peterson, Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada	Dr Martha Brumfield, Senior Vice President, Worldwide Regulatory Affairs, Pfizer Inc, USA
Marie-Helene Pinheiro, Scientific Administrator, Regulatory Affairs & Organisational Support Human Unit, EMEA, UK	Dr Ann Readman, Vice President, International Regulatory Affairs, AstraZeneca UK Ltd

Round Table Discussion Session 2 (Topics D-E):

Moderator: **Dr Justina Molzon**, Associate Director, International Programs, CDER, Food and Drug Administration, USA

Chairpersons and **Rapporteurs** as above, except that:

Alistair Davidson, Vice President, International Regulatory Affairs, GlaxoSmithKline R&D Ltd, UK replaced David Jefferys

TOPIC A: Models for Review Procedures and Types of Scientific Assessment

A1 Types of assessment

Conclusions

It was agreed that **multiple reviews by different authorities** of the core ('safety, quality and efficacy') scientific evidence for a new drug substance is not a good use of limited agency resources. By recognising the basic scientific review by at least two reference agencies, regulatory resources can be focused on the benefit-risk assessment of the finished product and its labelling, for the local market and on such activities as pharmacovigilance.

Discussion points

It was agreed that the capability for carrying out **a full review** of NAS applications was **not** a realistic or useful goal for all regulatory agencies, especially if a wider view of all UN countries is taken. Even within the EU, not all countries undertake such reviews but recognise reviews undertaken by the EMEA or other member states.

Regulatory agencies worldwide have higher priorities in terms of working with health authorities on ensuring supply lines, counteracting counterfeit medicines and handling safety alerts. It was, however, recognised that agencies in countries with a **local pharmaceutical industry** must develop the capability to assess any new products (of herbal or other origin) emanating from national companies.

Abridged and **verification assessments** are a practical alternative to multiple full assessments, where the 'core' data is assessed by reference agencies and the local agency focuses on factors relevant to the local market, e.g., labelling and quality assurance.

The question of whether companies could do more to assist this type of assessment was discussed, for example by providing more information on differences between their **products in different markets**. It was, however, pointed out that the days are 'long gone' when multinational companies had differences in the composition or quality of products marketed globally, even when different manufacturing sites are used.

Companies also operate on the basis of a **core data sheet** that is defined during the development process for a new medicine. Minor differences may arise as a result of national requirements, e.g., for class labelling, but companies would be willing to share information on such differences. There were concerns, however, about overburdening national agencies with information.

A2. An 'ideal' review process map

Conclusions

A common model or 'review map' for the sequence in which the different steps in a review are carried out is not a current priority. The focus should be on improving current systems rather than pressing for immediate, radical changes such as parallel rather than sequential review processes.

Discussion points

It was suggested that a long-term goal (possibly 20 years or more) might be common review sequences in order to improve standardisation of review processes, globally.

It was agreed that, as a general principle, **parallel rather than sequential** review paths were preferable but it was recognised that there are national systems that work efficiently and within relatively short timelines using a sequential review (quality followed by safety and efficacy or *vice versa*).

The role of **external experts** (non-agency individuals or committees) was discussed and it was agreed that these were very valuable but not necessarily *essential* to the review process. Those who still have 'hands on' experience of the laboratory bench, analytical work and clinical studies can make a very useful contribution to discussions but agencies also operate satisfactorily with only internal assessors. It was noted that employing part time assessors that maintain an external role e.g., as clinicians, also had advantages.

Eliminating backlogs and reducing queue times were seen, by industry, as an important goal for all agencies but it was agreed that speed and reduced review times are not the first priority. The quality of the review and other issues, such as ensuring that GMP standards are enforced were recognised as having equal importance.

Related to the speed of review was the question of **company response times** and the industry recognised its responsibility to deal promptly with agencies' requests for further information.

A3. Benefit Risk Assessment

Conclusions

Benefits would arise from **harmonisation of the criteria** for the benefit-risk assessment of new products, and may be feasible at a regional level but this is **not** a realistic international goal for the foreseeable future as such assessments remain subjective and are influenced by differences in health care systems, clinical practices and other cultural and historical differences.

Discussion points

It was, nonetheless agreed that the assessment of risk-benefit is the **key to a quality review** and that all other factors contribute to this assessment. It was noted that some countries currently appear to place more emphasis on, for example, product quality and CMC data and rely on the benefit risk assessment carried out by the reference country/countries. Concerns about poor quality and counterfeit products, however, also relate to assessment of risk at a local level.

It was hoped that some degree of **regional harmonisation**, for example in the Asia Pacific region or Latin America might be a feasible as a long-term objective.

Training in benefit-risk assessment and the relevance of local factors (e.g., ethnic and genetic factors, disease prevalence etc) would be a useful first step in achieving a more harmonised approach.

TOPIC B: Evidence of authorisation by other Agencies

B1. The Certificate of a Pharmaceutical Product (CPP)

Conclusions

The CPP, issued in accordance with the *WHO Certification scheme on the quality of pharmaceutical products moving in international commerce* still has a recognised role in the global registration of medicines but radical changes to its format and scope are recommended.

- Acceptance of an **electronic CPP** and less reliance on original paper documentation is urgently needed to reflect the current technological environment;
- There should be a **separation of the role of the CPP** as a GMP certificate and as evidence of authorisation in the issuing country;
- A requirement for **marketing in the issuing country** should be removed from the CPP.

It was further recommended that the WHO ICDRA meetings and the ICH Global Cooperation Group should have a role in discussions to rationalise and update the use of the CPP and the Scheme in general.

Discussion points

The regulatory requirements for a CPP are still regarded as a major hurdle to pharmaceutical companies in the **global roll-out** of new medicines. Countries can be relegated to the second and third wave in the launch of a new product because of the need to obtain and provide CPPs, even where the local agency is capable of carrying out the appropriate assessment.

The scope of the CPP has extended over the years and it now acts as an assurance that the product is manufactured according to **GMP** (its original role) and evidence of **prior authorisation** as well as providing information on the **marketing status** in the issuing country.

All three would be better handled separately:

- **GMP:** Requirements for a CPP from the 'source' country from which the product is imported and where it is actually manufactured can be a major problem if the product is not actually registered in that country. There are also major problems for companies where a CPP from the FDA is a regulatory requirement in the importing country but the product, although approved in the US, is manufactured elsewhere.

The current Certification Scheme has not kept abreast of current practices whereby companies have multiple manufacturing sites all operating to the same GMP standards and products may be sourced from different sites to ensure uninterrupted supply. Membership for PIC/S or recognition of inspections carried out under the scheme are a more up-to-date way of dealing with GMP certification.

- **Prior authorisation:** There are sound alternatives to the CPP through which regulatory agencies can obtain assurances of the regulatory status of products in different countries. This is discussed in more detail below.
- **Marketing status:** Even in the major markets, the launch of a new product can be delayed. If obtaining a CPP is held up until the product is on the market in the issuing country, this will effectively delay the submission of the product in other countries.

It was agreed that formal requirements for the CPP to be legalised through the local consulate of Embassy of the importing country are outmoded and unnecessary although it was acknowledged that changes in legislation would be required to bring this about.

B2 Alternatives to the CPP as evidence of registration

Conclusions

The type of evidence that is required about registration by other agencies should be more flexible and agencies that have the capability to carry out a full assessment should take steps to eliminate rigid CPP requirements from their review procedures. Information on existing authorisations that is posted on the Internet websites for the major agencies is a reliable substitute for a CPP in terms of accepting applications for review and validating the status of the product.

Where national regulations preclude such flexibility the agencies should initiate action and give their support to bring about local legislative change.

Discussion points

The extent of an agency's reliance on the CPP depends on the type of review that is carried out by the importing country but there was concern that the roll-out of new medicines to countries with more developed regulatory agencies could be delayed by rigid certification requirements.

There was unanimous agreement that the **information provided on the websites** of well-established agencies such as US FDA and the EMEA has a major role in providing assurances to other agencies on the regulatory status of products. Copies of letters of authorisation and evidence from websites should obviate the need for a CPP to be provided at the time of submission for new medicines.

It was noted that **letters of authorisation** from an agency are confidential and that permission is required before they can be transmitted to other parties. Also, that such letters provide confirmation of the authorisation status but do not necessarily include the detail of a CPP and will differ in format from agency to agency.

It was acknowledged that not all agencies have the infrastructure to allow all staff to make full use of the Internet and that some **training** might be required to make staff aware of the information that is available from agency websites.

Some concern was expressed about whether importing countries can easily obtain information about the **post-authorisation commitments** (PACs) attached to some approvals. Companies have a primary responsibility for ensuring that they provide clear information on requests for additional information agreed as PACs on previous applications. Training may, again, be required

to make staff aware of the way in which PAC procedures operate and ensure that they are not confused with *conditional authorisations*.

It was noted that many key agencies run **secondment schemes** to train staff from other agencies and help them become familiar with such issues.

On the need for **changes in legislation** to enable a more flexible approach to the CPP and alternative sources of information it was suggested that local industry and industry associations could have an advocacy role in discussions at a political level. The agencies, however, made it clear that any initiatives to reform the law must come from within the agency itself and have the 'buy in' of those directly concerned.

It was noted that the East European countries in CADREAC (Collaboration Agreement between Drug Regulatory Authorities in EU Associated Countries) had faced the challenge of **removing legal requirements** for a CPP and had removed certification requirements in exchange for use of the information in the European Pharmaceutical Assessment Reports (EPARs) issued by the EMEA.

Topic C: Exchange of assessment reports

C1. Better use of reference agency reports

Conclusions

The reports published by the major agencies (e.g., the EMEA EPARs and the US FDA Summary Reports) are a valuable resource for other agencies but do not (and are not intended to) provide the detail of information needed by other agencies carrying out a detailed review of the same product. Where such detail is needed the agencies should work under confidentiality agreements and exchange full assessment reports, with the consent of the company concerned.

Discussion points

Companies are generally willing to cooperate in giving **consent** for the exchange of assessment reports but it is important that such schemes contribute to the quality and efficiency of the review and do not just become an additional regulatory requirement with no visible benefit to the sponsor.

Of particular concern is the need to ensure **confidentiality and intellectual property** protection for commercially sensitive information, especially in the CMC sections of applications.

Language barriers and the need for translations were not seen as an obstacle as such matters are accommodated by companies in the way in which applications are filed around the world. The need to ensure the quality of translations is, of course, essential.

Agencies emphasised the benefits of **establishing a special relationship** with the major 'reference' agencies (including memoranda of understanding) with the potential to work alongside them in the assessment of major applications.

C2. Regional exchange schemes

Conclusions

It was agreed that the exchange of assessment reports between regulatory authorities in the same region (e.g., ASEAN members) would be a valuable step towards building mutual confidence between agencies and increasing harmonisation. It would not, however, be a *substitute* for receiving assessment reports from the reference agencies which first assessed the new medicines under review.

Discussion points

Lessons could be learnt from the EU experience. A starting point is to put in place **memoranda of understanding** and confidentiality agreements and to begin with an informal exchange of reports.

Joint assessments could be seen as a logical progression from regional schemes for the exchange of reports but this was not seen as a realistic short-term goal. Joint assessments and the mutual recognition of evaluations work in the EU because of common legislation which does not currently exist in other regions.

Reference was made to the Pharmaceutical Evaluation Report 'PER Scheme' operated by EFTA from 1980 to 2001 and the points on its operation, benefits drawbacks that were presented earlier in the Workshop (see summary in *Box 1*)

The **benefits** of regional schemes for exchanging assessment reports include the potential for increasing harmonisation of technical requirements, encouraging work-sharing and the possibility of reducing the burden of multiple questions to industry. The **barriers** were felt to lie in identifying a common denominator that does not escalate regulatory requirements. Harmonisation also requires additional resources and there must be the political will to support such initiatives.

To a certain extent there were parallels with the **PIC/S Scheme** for GMP inspection reports on manufacturing sites in that exchange of assessment reports would help to build confidence in, and understanding of, the review procedures of other agencies. There are few other similarities, however, as the PIC/S scheme is based on agreed international standards that are not yet established for the review of safety and efficacy.

C3. The need for a common assessment template

Conclusions

It was recommended that the CMR International Institute should include, in its future work programme, a study of similarities and differences in the clinical sections of the assessment templates from a number of different agencies. It was agreed, however, that it was premature and over-ambitious to consider a project for internationally harmonised assessment template for new medicines, at this stage.

Discussion points

The **assessment templates** developed by different agencies serve different purposes, for example as a response to calls for greater transparency (e.g., the EPAR) or to guide internal and external assessors. The current differences between data requirements (especially for CMC) and review procedures are so great that it would not be the best use of resources to try to develop a common format.

If regional schemes for exchange of assessment reports are considered, however, a common assessment template might be an important element in making progress towards greater mutual understanding.

Topic D: Building Quality into the Review Process

D1. Quality standards and objectives

Conclusions

All agencies can improve the quality of their working practices but the standards set for building quality into the review should be realistic and '**fit for purpose**'. Targets need to be realistic and not set so high that they impede efficiency.

Discussion points

Whilst it is too early to consider international harmonisation of **Good Regulatory Review Practices** (GRP) it was agreed that there are general principles of consistency, transparency and predictability that could be identified and defined as the basis for drawing up local GRP.

All agencies can improve the quality of their working practices but the standards set for building quality into the review should be realistic and '**fit for purpose**'. Targets need to be realistic and not set so tight that they impede efficiency.

Quality is independent of the complexity of the review purpose. It is possible to have high quality but minimal review procedures, for example in an assessment that consists only of 'validating' the regulatory status of a product.

D2. Transparency

Conclusions

Building transparency into the review process drives improvements in the system to the ultimate benefit of the public and patient. Transparency requires political will as resources are needed but the investment has very positive benefits.

Discussion points

It would be naïve to assume that transparency costs nothing but greater openness and public information on the regulatory system is often **demanded by the consumers** that the agencies serve.

An important element of transparency is the openness of **interactions between agencies and companies** before and during the assessment process. It was agreed that such interactions benefit not only the companies but also the assessors themselves. The **rules of engagement** must, however, be defined to set the parameters for such meetings and communications.

Topic E: Improving the Quality of Review Processes

E1. Project Management

Conclusions

Sound Project Management fundamental to improving and monitoring the quality of the review process. Two elements were identified as being of particular benefit:

- Providing a single point of contact within the agency with whom the company can communicate;
- Establishing a procedure for resolving contentious issues during the review by bringing together internal reviewers, the sponsor and, as appropriate, external advisors in order to avoid an impasse and subsequent appeal process

Discussion points

Project Management is a key factor in establishing an efficient regulatory agency but the level of implementation may differ according to the type of agency and availability of resources. Significant benefits can be gained from relatively minor management changes and basic performance indicators **without high resource implications**.

Changes in the culture of an organisation may be required in order to accept the principles and practicalities of project management. **Senior management** must be committed to the concept and time must be allowed for new systems to be accepted. **Improved staff morale** is one of the benefits that can be expected once positive results are seen in terms of efficiency and increased productivity.

E2. Feedback

Conclusions

It was recommended that all agencies should introduce mechanisms, no matter how rudimentary, of exchanging views and feedback with companies after the assessment of a major application for a new medicine.

Discussion points

Reference was made to the CMR International Institute project to develop 'scorecards' for feedback between regulatory agencies and companies following the review of a new drug application.

It was acknowledged that the concept of partnership between government and industry and the ability to accept criticism may be barriers to feedback systems in some countries/regions. These can be overcome with political will and the acceptance of greater transparency. It is important to emphasise, however, that the feedback must be two-way with the ability to comment on both company and agency performance.

E3. Tracking and monitoring systems

Conclusions

Good application tracking systems and effective project management are complimentary and inter-dependent. It was recommended that agencies with the facilities to monitor timelines and provide feedback should publish summaries of their findings and share these with industry and other interested observers, on an annual basis as part of the learning process.

Discussion points

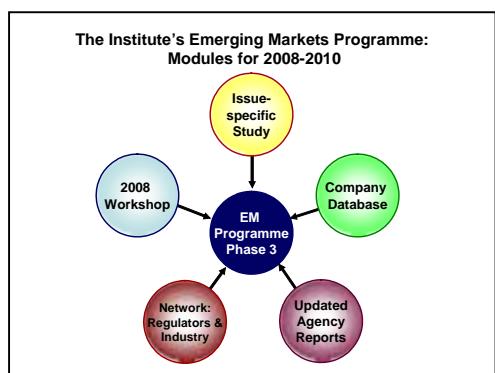
Setting and adhering to timing and performance **targets** are an important measure of the quality of a review process but it must be remembered that industry also has a responsibility to adhere to timelines when responding to requests for additional information.

Electronic application tracking systems are only as good as the Project Management system within which they operate. Technology cannot replace **trained and committed staff**.

3. THE WAY FORWARD

The Workshop concluded with a presentation by **Dr Neil McAuslane**, *Director of the Institute for Regulatory Science* on the Institute's current study of the regulation of new medicines in the Emerging Markets and possible future directions.

The project started in 2004 and the first and second phases provided a background to the first Institute Workshop on the Emerging Markets in March 2006. The initial studies sought a better understanding of the regulatory environment outside the ICH-affiliated regions and looked at potential changes that could expedite patient access to new medicines through improved approval systems and reduced regulatory barriers. The third phase focused on review models, types of scientific assessment and quality issues that were discussed at the current Workshop.



It is envisaged that the next phase of the Emerging Market's Project will have five component modules as illustrated in the slide:

- **The Company Database** of timelines and experience in registering new medicines will be maintained;
- **The Agency Reports** on key features of the review systems will be updated
- **The Network** of regulators in the Emerging Markets and concerned company experts will be enhanced
- **An Institute Workshop** is planned for 2008
- **An issue-specific Study** will be undertaken.

Topics for the issue-specific research project had been suggested by companies and regulators and these were under discussion at the time of the Workshop. These included: **Clinical trial approval** systems that accommodate arrangements for global clinical trials; Best practices for making **benefit-risk decisions**; A **focused study** on regulation in India and in China (to reflect the particular interest in these countries); Exchange of **review reports** and other opportunities for partnership between agencies; **Manufacturing issues** and the regulatory challenge of the trend towards multiple international production sites.

The selection of future studies will be made in accordance with the overall objectives of informing thinking, creating a forum for better mutual understanding of global regulatory issues and helping to encourage best practices for moving the regulation of medicines forward.

WORKSHOP PROGRAMME

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CMR International Institute Workshop

THE EMERGING MARKETS: MODELS OF BEST PRACTICE FOR THE REVIEW OF NEW MEDICINES

SECTION 3: PRESENTATION SUMMARIES

SESSION 1: REGULATORY MODELS FOR THE REGISTRATION OF NEW MEDICINES

This Session was chaired by **Professor Robert Peterson**, *Professor of Paediatrics, University of British Columbia, Canada*, and started with an overview of the options for the review of new medicines that have evolved over the years in different parts of the world. It continued with reports and discussion of the models adopted by Argentina, Indonesia, India, China and Singapore.

OVERVIEW OF REVIEW OPTIONS

Dr David Jefferys, *Vice President, Global Regulatory Affairs, Eisai R&D Company Ltd, UK*, discussed past, current and potential future models for the reviewing new medicines in a resource-constrained environment.

Medicines are being brought to market in a pharmaceutical environment where the pressures on companies include: the time and cost of development; the need to expand current markets and to make products available in new markets. Against this background is a common agenda for both industry and regulators of fulfilling public health demands and addressing unmet medical needs.

The global market is changing, in particular, the increased importance of South East Asia which currently comprises 56% of the world's population. In 2010 China will be the fifth largest pharma market and South Korea will be the eleventh.

A primary need is to reduce the 'drug lag' in the emerging markets and to address the evaluation costs to both companies and regulators, especially through more efficient use of experienced reviewers and regulatory affairs personnel, of which there is a global shortage.

Review Models

Five 'models' for the evaluation of pharmaceutical products were identified: primary, secondary and tertiary reviews and procedures that involve shared/joint evaluations and the use of the CPP (see box).

The **primary review** is the classic procedure historically used by most major agencies. One agency carried out a complete, self-standing review and this would be repeated sequentially, or in parallel by other major

Review models

Types of evaluation

Primary review

- Single complete, independent review
- Examples: FDA, PMDA new drug reviews

Secondary review

- Partial, focused evaluation carried out after a primary evaluation has been undertaken elsewhere
- Examples: EU mutual recognition and decentralised procedures

Tertiary review

- Acceptance of a review carried out elsewhere
- Examples: New GCC process; objective of the EU Mutual recognition procedure

Review process

Shared/Joint review

- Collaboration between different agencies on the same product
- Example: EMEA centralised process

CPP exchange

- Use of evidence of regulatory status and quality in country of export
- Support for secondary and tertiary reviews

agencies. FDA, PMDA and Health Canada carry out primary reviews but the EU member states no longer undertake repeated, full assessments of the same dossier.

In a **secondary review** the agency has the assessment report of another agency and, rather than starting afresh, carry out a partial, focused ('targeted') assessment looking only at certain aspects. Examples in the EU include the Mutual Recognition and the Decentralised procedures where the Reference Member State (RMS) carries out the primary review and the Concerned Member States (CMS) carry out a secondary review to ensure that the product meets national requirements and criteria.

A **tertiary review** is one where the regulatory agency takes the report, following the assessment by another agency without further assessment and refers it to, for example, an expert advisory committee. An example is the Gulf Collaborative Council Scheme in the Middle East. This is also, ideally, the model towards which the EU has been moving with true Mutual Recognition of the RMS decision by each CMS.

A key issue in both secondary and tertiary reviews, where one agency has to rely on the assessment of another is confidence building. The EU has had over 30 years experience, since 1965, of learning to accept the assessments carried out by other agencies.

Shared reviews involve collaboration between two or more agencies reviewing the same dossier. The main example from the EU is the system of a *Rapporteur* and *Co-Rapporteur* from different member states assessing the same dossier under the Centralised Procedure. The EMEA is also establishing multi-national, multisource assessment teams for specialised products and the revised pharmaceutical legislation has provision for the EMEA to undertake reviews jointly with WHO.

There is limited international experience of shared reviews at present but FDA and PMDA have experience with devices and TGA and Health Canada have an initiative for the review of biological products.

The **Certificate of a Pharmaceutical Product** (CPP) can have an important role in both secondary and tertiary reviews in the developing and emerging countries to provide assurance of prior authorisation and the outcome of the evaluation. It should be a simple system to operate but there are concerns about the way the scheme is operating, how it might be better used and, particularly, about the way it could evolve.

Applications can often be delayed by several months while CPPs are issued. Why, in an electronic age can certificates not be obtained 'in real time' via secure internet links and website?

Exchange of Assessment Reports

Secondary and Tertiary reviews depend upon obtaining information on primary assessments carried out elsewhere and, as noted, building confidence in such reviews. The **PER Scheme** for the exchange of *Pharmaceutical Evaluation Reports* was an important part of the 'evolution' of

such processes among the more developed agencies. Set up by EFTA¹, in 1980 (see box) the scheme allowed assessment reports to be exchanged initially between European countries and later extended to Australia, New Zealand, South Africa and countries emerging from the Soviet bloc.

This was an 'open' exchange scheme in which industry retained the rights to see the reports, to comment and (on very rare occasions) refuse to allow release of the report. Translation of the reports was an industry obligation. The PER scheme promoted the development of evaluation guidelines, assessment checklists and templates and mutual confidentiality agreements. During its existence, the scheme shortened assessment times by a mean 40 days and reduced, by an estimated 30%, the resource requirements of

Per Scheme

Historical background

Operated 1980 to 2001

Sharing of assessment reports and feedback

Peak involvement of 19 countries

600 reports exchanged

Initial phase: circulation of approved products list and final assessments

Later phase: circulation of pending approval list

Limited extension to line extensions and supplementary filings

¹ European Free Trade Association of countries (e.g., Switzerland) that were in Europe but not members of the EU. Membership has decreased with the expansion of EU membership

recipient authorities. The scheme had strong support from industry; and increased understanding and co-operation between agencies.

The scheme was abandoned primarily because the EU participants found it redundant once European Pharmaceutical Evaluation Reports (EPARs) were developed and available to agencies. There are opportunities to be explored for the exchange of evaluation reports in the Asia Pacific Economic Community (APEC) region and to learn from past experiences. One possibility would be to include life cycle management and pharmacovigilance assessments in the scheme. A regional scheme involving ethnically similar populations could also help address some of the issues raised by the ICH E5 guideline on *Ethnic Factors in the Acceptability of Foreign Clinical Data* by exploring the significance of differences in the APEC region, for example focusing on pharmacodynamic differences that are linked to adverse events. Understanding ethnic differences will also be assisted by the increased trend towards multinational, multiregional trials and the adoption of early inter-ethnic dose ranging studies.

In conclusion, the issues to be addressed by this Workshop when looking at ways to improve review procedures include: More rational use of resources; Reduction of multiple reviews; Ways to reduce the drug lag in some emerging markets and; Focusing resources on the priority areas of medical need.

INSTITUTE STUDY

Dr Neil McAuslane, *Director of the Institute for Regulatory Science, CMR International*, presented a cross-comparison between the 13 regulatory agencies that had been studied in the third phase of the CMR International Institute for Regulatory Science's study on the Emerging Markets (see Annex 3). He discussed the section of the study that had looked at differences and similarities between the assessment models and process maps used by different agencies and the way in which information on prior authorisation elsewhere was being used.

When the median approval times for new active substances (NAS) calculated from data supplied by the 13 participating companies are compared for 2004-2006, they vary, widely around an overall median of 290 calendar days, from the 165 days (Argentina) to 2095 days (Egypt). The approval time is not, however, the only factor to have an impact on the 'roll out' time that it takes for new medicines to reach the different markets compared with first approval anywhere, usually in an ICH country. There is a critical time interval between approval by the first authority and subsequent submission for approval in another market. For the countries studied, this ranged from minimal or no time elapsing in some Latin American countries to delays of over a year.

The main components affecting the delay in submitting an application are national application requirements (e.g., the need for a CPP, requirements for local clinical trials) and company strategy in selecting priority markets. The differing national approval times are then related to the type of review carried out by the agency.

One of the objectives of the Institute study was to provide a better insight into these factors.

Types of assessment

One of the recommendations from the Institute Workshop held in Geneva, March 2006 was to look at the types of review carried out by agencies. Assessment types were classified, based on the 'Singapore model' as Type 1 'verification', Type 2 'abridged' and Type 3 'full' (see Annex 2 Topic A). More than one type of assessment is available in some countries when all applications are considered but, in terms of the assessment predominantly used for NAS and major line extension (MLE) applications the results were as follows. Argentina was the only country using a Type 1 assessment while five countries (Mexico, Egypt, Saudi Arabia, Malaysia and Singapore) used type 2. Although seven countries (Brazil, South Africa, China, India, Indonesia, South Korea and Taiwan) routinely applied a full assessment process to NAS applications only in South Africa is this completely self-standing as the other countries still require evidence of approval in a reference country before final local authorisation.

Evidence of authorisation elsewhere

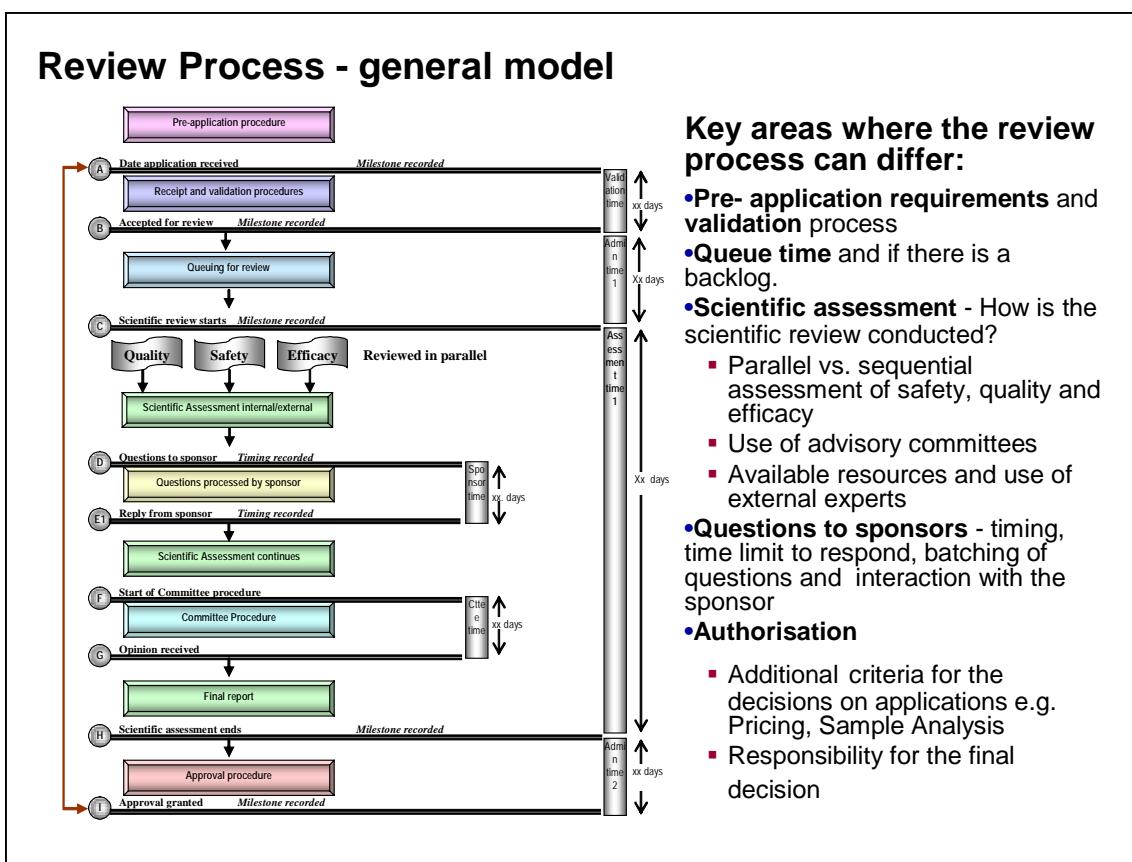
The Certificate of a Pharmaceutical Product (CPP) remains the most common requirement but timing and requirements vary. The CPP is not required in South Africa or in Singapore and Indonesia, when they carry out a full, Type 3b, review. When Singapore does require evidence of prior approval there is some flexibility and evidence other than the CPP can be accepted.

The CPP is required at the time of submission by Argentina, Egypt and Saudi Arabia but in Brazil and most of the Asia Pacific countries studied it can be submitted later, before authorisation. The need for legalisation of the CPP through an Embassy or Consulate in the exporting country remains a requirement in Brazil, Egypt, Saudi Arabia and Taiwan.

Review Process Models

A general 'model' was drawn up to map the stages in the review process as they most frequently take place (see slide). Agencies were asked questions based on this model and individual processes were "mapped" accordingly. The model also indicates the different stages at which timing might be recorded to allow targets and timelines to be set.

Although an overall similarity between countries and regions was found, there are key areas where notable differences were found between processes, as noted on the slide. Mexico has introduced a voluntary **pre-application** procedure that allows companies the opportunity to discuss NAS applications with a committee of experts prior to submission. In China, a full IND and clinical development programme must be undertaken in the country before an application for marketing can be made



Queue times can vary widely with applications being picked up for review almost immediately in some countries (e.g., Taiwan and South Korea) or waiting 6 months to a year in others.

The classic **review sequence** is to carry out a parallel review with the quality, safety and efficacy sections of the application being assessed at the same time. Examples of a sequential review were reported from Indonesia, where safety and efficacy must be approved by the expert committee before resources are assigned to the quality section and in Mexico where quality is assessed before the review of safety and efficacy commences.

Procedures for the final **authorisation procedure** differ and can cause delays if matters other than the scientific review need to be finalised before the authorisation is issued. Three authorities, Brazil, Egypt and Saudi Arabia require pricing agreements before authorisation and sample analysis is required in Egypt and Saudi Arabia and for certain biologicals in Brazil and Mexico.

Targets: As noted, the process map indicates the review stages for which targets can be set. Although these are important to making the review more predictable and project management more efficient, not all agencies had documented targets. For validation the targets ranged from none to six weeks, for scientific assessment from none to 160 working days, for the authorisation procedure from none to one month. Targets for overall approval times ranged from none to a year and different targets applied in countries (e.g., Singapore) where different assessment routes could be followed.

Positive and negative factors

Both agencies and industry were asked for their viewpoint on factors that contribute to and factors that impede the effectiveness and efficiency of the review, although the factors that impede were, in effect, the opposite of the positive factors. The positive factors were: Political will; Adequate resources; Training (and retaining) qualified and experienced staff; Electronic tracking system and; Standardisation of the review process through GRP and SOPs. Complete submissions from industry are also a major contribution to the process.

Companies concerns fell into four areas. **Evidence of registration elsewhere** needs to be rationalised and the timing and requirements for the CPP continues to cause concern. Transparency and communication during the **review process** are perceived as important benefits as are targets and optional procedures (as in Singapore). **Data requirements** should be within international norms (i.e., ICH guidelines for new medicines) and other issues such as pricing and site inspections should be separated from the scientific review process. The **organisation** of the agency should be adequately resourced and operate with as much flexibility and as little bureaucracy as possible.

Conclusion

The regulatory aspirations, barriers and priorities are essentially similar across agencies. The review steps are also similar across agencies although there are major differences in the assessment process.

Regulatory review procedures and requirements are undergoing rapid change in the thirteen countries studied and both authorities and companies are seeking to understand better the factors that impact on performance.

Most Agencies are using risk stratification methods for their review of new medicines, based on the level of regulatory scrutiny the product has already undergone elsewhere. The challenge is how best to evolve these methods to ensure timely access to patients of new medicines within an appropriate benefit/risk decision making process

ARGENTINA

Analía Pérez, Director of Drug Evaluation, Administración Nacional de Medicamentos Alimentos y Tecnología Médica (ANMAT), discussed the way in which the Agency in Argentina has adopted a review process that uses evidence of registration in specified ICH countries as a key factor in expediting the review of new medicines and thus speeding up patient access to new therapies.

In Argentina, ANMAT, with a staff of over 650 and a budget of US \$4.1 million, controls the quality of medicines in accordance with World Health Organization (WHO) Good Manufacturing Practices (GMP) 2004, Good Distribution Practices (GDP) and Good Laboratory Practices (GLP) and, from January 2008, will participate in PIC/S.

The agency's laboratories operate a pharmacosurveillance system and there is a counterfeit control program. For multisource 'similar' and generic products there is a bioequivalence/bioavailability programme.

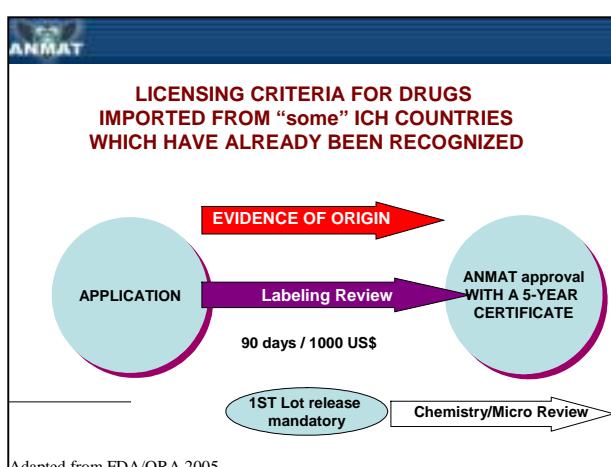
An international manufacturer must be represented in Argentina by a local company that has a local laboratory to control the final product. Some control, however, may be delegated to third parties.

There are three routes for the evaluation of medicinal products:

Full review for those products that have yet to be approved by any regulatory agency. (There is currently little experience of this process);

Abridged evaluation for 'similar products' where the focus is on quality;

Verification evaluation for new drugs that have been approved by a 'benchmark' regulatory agency. These, for historic reasons, are the agencies in the US, Israel, Canada, Austria, Germany, France, UK, Belgium, Denmark, Spain, and Italy. For the verification procedure evidence of origin and a labelling review are required and, if approved, ANMAT issues a 5-year certificate that may be renewed. There is a mandatory batch release process for the first lot which involves chemistry and microbiology testing.



The verification process takes 90 days (see slide), and a fee of US \$1000 is required. The focus is on reviewing the package insert and ensuring that the product is consumed in the country of origin and not produced *for export only*.

As the verification process is so rapid there is no necessity for a 'fast track' system for urgently needed products and designated 'orphan drugs' that are licensed elsewhere undergo the same process. ANMAT has an electronic process for scanning and tracking applications which assists in administration and monitoring.

A possible disadvantage of the rapid processing of new drugs is that there is very little time lag between the ICH markets and Argentina, which requires special attention to pharmacosurveillance.

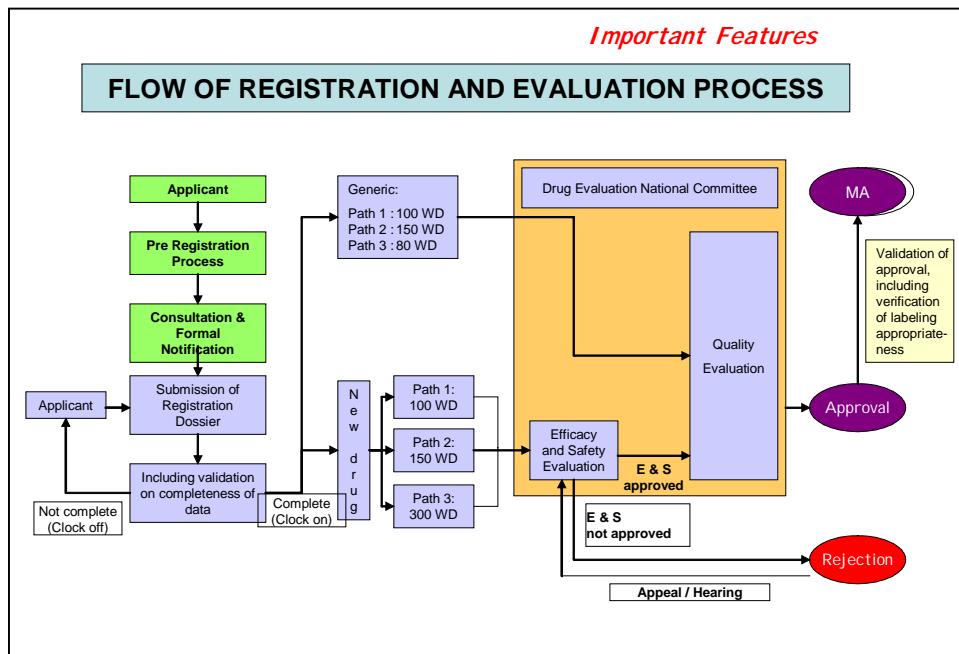
Future challenges are to improve the electronic licensing process; provide new guidelines for surveillance during the first 5 years of marketing; publish new guidelines for updating licenses; and review requirements for local control and/or the need for international inspection of certain products.

INDONESIA

Lucky Slamet, *Director of Therapeutic Products, Narcotics, Psychotropic, and Addictive Substance Control, National Agency of Drug and Food Control (NADFC)*, discussed the review model in Indonesia, which, for new active substances, follows the same review process (see slide) but has different data requirements according to the nature of the product. This affects the speed of review, with priority being given to products that address urgent medical needs. The review process itself is unusual in operating a *sequential* review with the preclinical and clinical data assessed first and resources only being assigned to the review of quality (CMC) data once the experts have accepted the product on safety and efficacy grounds.

Indonesia's registration system for drugs and biologicals anticipates Global Harmonisation trends and is based on risk assessment (safety, efficacy, and labelling) and the actual needs of the public health. Psychotropics must show superiority over registered drugs; the drugs for national health

programs (e.g., vaccines and family planning) must undergo clinical trials; and pricing must be competitive, both internally and externally. Quality control is according to GMP standards. Requirements are similar for imported and domestic products.



New drugs and biologicals follow one of three pathways and the requirements for submitting the CPP depend on the path:

Path 1 products are life-saving and breakthrough drugs, including orphan drugs (approval within 100 work days). The **CPP** need not be submitted at time of application.

Path 2 products are those already marketed in 'harmonised' (ICH compliant) countries (approval within 150 work days). The **CPP** must be submitted with the application;

Path 3 is for other new drugs or biologicals, e.g., parallel registration of products not yet authorised elsewhere (approval within 300 work days). The **CPP** may be submitted after application but must be available before approval.

There are also three pathways for the review of generic products: *Path 1* is for generics essential for national health programs (approval within 100 work days); *Path 2* is for other generics for use in Indonesia (approval within 150 work days); *Path 3* is for generics for export only (approval within 80 working days). In all cases, the CPP for imported generics is required at the time that the application is submitted.

The timing for evaluation of NASs had been recorded for 2002-2007 and in 2006, 91% of Path 1 drugs, 67% of Path 2 drugs, and 96% of Path 3 drugs were approved on time. Approval times were longer in 2007 with 72% of Path 1 and 50% of Path 2 NASs being approved on time. This was due to agency staffing problems but efficiency is also a function of completeness of the documents submitted. Applications must be submitted in a format that meets national standards and complies with the ASEAN (Association of Southeast Asian Nations Common Technical Document (CTD), but the ICH CTD format is also currently accepted.

A study of success rates in relation to the source of the CPP had been made for Path 2 products approved between 2001 and September 2007 and showed the following: 66.7% approvals for CPPs from Asia; 82.5% for US and Canada; 93.5% for European Medicines Agency (EMEA); 96.2% for non-EMEA Europe; and 100% for Australia and New Zealand.

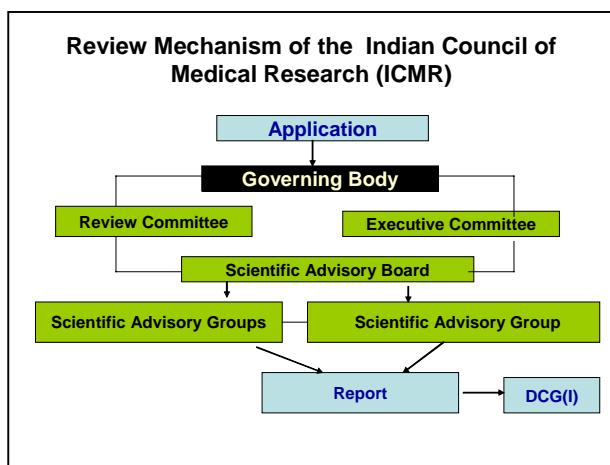
The challenges for the future include establishing early dialogue with companies over requirements for registration and developing country agencies that authorise products (e.g., vaccines) that are not widely used elsewhere have a particular challenge in carrying out post-marketing surveillance and studies.

INDIA

Dr Eswara Reddy, *Office of Deputy Drugs Controller (India), Central Drugs Standard Control Organisation (CDSCO)*, described the way in which the Indian authorities undertake a full review of data on new medicines which utilises the expertise of the Indian Council of Medical Research (ICMR). Clinical trials must be undertaken in India in order to obtain approval for new products, although there is a move towards facilitating the registration of medicines that are part of a global clinical development programme.

India's pharmaceutical industry is ranked 4th in the world in terms of volume and 13th in terms of value (US \$10 billion; \$4.3 billion exported). Formulations comprise 55% and Active Pharmaceutical ingredients (APIs) 45% of its pharmaceutical exports. India has the largest number of US FDA-approved plants outside of the US. Its business model revolves around contract research, contract manufacturing, and co-marketing alliances.

The pharmaceutical industry is highly regulated for safety, efficacy, and quality; drug price control; and patent protection. India's Drug Controller General has the responsibilities of drafting legislation; approving new drugs; controlling the import and export of drugs; establishing standards; testing drugs; and coordinating activities. State responsibilities include the licensing of drugs and cosmetics; monitoring quality; investigations and prosecutions; and administrative actions. The federal and state governments share the joint responsibilities for Central Licence Approving authority (CLAA) activities and issuing CPPs.



The ICMR has the mandate to undertake and support basic, epidemiological, applied, and operational research in the areas of national public health. Clinical trials are regulated according to GCP and ICMR guidelines, as well as the Declaration of Helsinki. GLP, a National Pharmacovigilance Programme, and bioequivalence and bioavailability guidelines are also implemented.

For drugs discovered outside India, Phase I data must be submitted in a marketing application and may need to be repeated in India. Some Phase II and/or Phase III studies also need to be conducted in India. Upon application, small quantities of drugs can be imported for examination, test, or analysis. Drugs for life-threatening, serious, or special diseases may receive waivers for clinical and toxicological data.

New drug applications (NDAs) are submitted with documentation of chemical and pharmaceutical information; animal pharmacology; animal toxicology; clinical pharmacology; regulatory status in other countries; prescribing information; and samples and testing protocols.

Safety and efficacy are reviewed by advisory committees: ICMR, IND committee, Recombinant Drugs Advisory Committee (RDAC), and the Review Committee on Genetic Modification (RCGM) for recombinant DNA products. The key aspects of the review are efficacy, safety, dose response, exposure-response, dose adjustments for special populations, and drug interactions. The target maximum time for completion of the review process is 9 months but average approval times are 4 to 6 months for NDAs. Applications for trials that are part of global clinical trials are assessed in 4 to 6 weeks.

Best practices include definitive legislation, scientific support, transparency, quality management, guidelines for industry, and interaction with the applicant. Challenges that remain include inadequate staffing, training, clinical registry, data protection, and the archiving of documents.

Future developments include the establishment of a Central Drug Authority (CDA) to replace the CDSCO. A Bill has been introduced in parliament for the introduction of an autonomous body that would also take over some functions currently carried out at State level, including a central licensing system and licensing of Clinical Trial Sites.

CHINA

Dr Zili Li, Director of Clinical Research Operations – Asia Pacific/ Head of Regulatory Policy MSD China, acknowledged that the time taken to obtain authorisation for new medicines in China is a major cause for concern to companies, as well as the need to carry out local trials as an integral part of the marketing approval process. Dr Li pointed out that a factor in long review times is company response time and urged companies to acknowledge the changes that are taking place within SFDA and ensure that they are organised to respond to and interact with the agency in cooperative way.

The time for approval of imported drugs in China is 2.5 to 3 years but review process is CPP-dependent and cannot commence until approval is obtained elsewhere (see slide).

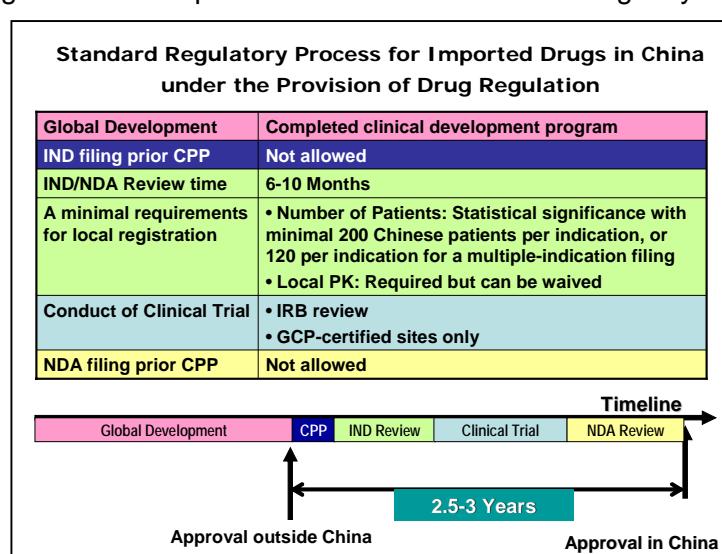
The 2005 revisions of the regulation attracted more multinational trials to China but, in practice, integration of China into global drug development was hindered by the time taken for clinical trial approval (>6 months) and the requirements for extensive data (not necessarily available at that stage) to be included in the submission.

The 2007 revisions failed to address this timeline issue in a significant manner since the technical review time was only reduced for a highly selected number of drugs (25% reduction). However, the agency did make a significant effort to align with international practice on, for example, the acceptance of the ICH-CTD format, more flexible documentation requirements for GMP and simplified sample testing. There are also changes aimed at building quality into the review and introducing a special review system that makes provision for consultation meetings with the sponsor, granting conditional approvals, and allowing the submission of further information during the review.

These changes impact the review of new drugs, especially those imported into China but it must be remembered that the State Food and Drug Administration (SFDA) and the Center for Drug Evaluation (CDE) are also dealing with large numbers of marketed products and marketing applications from domestic and generic manufacturers. A comparison of US FDA and China's SFDA showed that, in 2005, China's CDE had 120 employees to review 1113 new drugs and 8075 generic drugs whilst the US FDA's 1800 employees handled 20 new drugs and 344 generic drugs.

The implementation of tighter procedures for the review of new medicines has drastically reduced the number of applications filed by domestic producers but there remains a large majority of applications from within China compared with imported medicines.

Looking to the future the completely linear model shown in the slide should soon be 'yesterday's' model. Allowing multinational trials (either a global or regional approach) to commence in China before the CPP is available enables trials to be carried out that can also form part of the marketing application. Thus parallel development in China and globally is becoming more common ('Today's' model). For 'tomorrow's' model the vision is a science-based review carried out in parallel with global development where the agency sets realistic time limits for its technical review and requires only those information and data which are consistent with the stage of drug development. But industry must play its part by having sufficient local resources and scientific expertise to enhance the quality of submission in order to minimise the number of questions from the agency, and also by responding quickly to enquiries and providing the appropriate scientific responses within a fixed time frame. Otherwise the issue that is similar to FDA's multiple cycles of review will soon become a significant factor in prolonging the approval time for clinical trial applications and marketing applications.



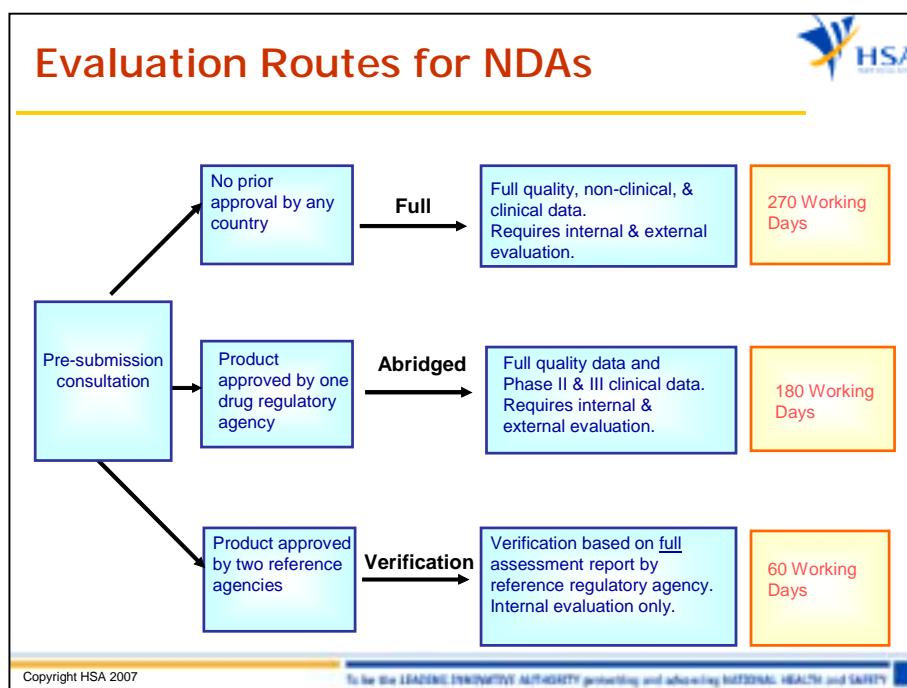
SINGAPORE

Dr Kian-Ming Lam, *Deputy Director (Corporate Operations), Health Sciences Authority (HSA), Singapore*, explained the way in which the regulatory system in Singapore uses different review models and has different data requirements according to 'risk-based' criteria. The selected model depends on the evidence of prior authorisation elsewhere, at the time of submission.

Singapore has 4.5 million citizens, comprising Chinese (75.2%), Malay (13.6%), Indian (8.8%), and others (2.4%). Singapore's HSA is unique in that it has an Applied Sciences Group, in addition to its Health Products Regulation Group and Health Services Group. In a changing and unstable environment, the HSA must consider crises and emergencies, including infectious diseases and natural disasters. It must strike a balance among role, policy, and resources. The HSA's approach is that no health product is 100% safe and that registration is not the same as certifying that a product is risk-free.

Following implementation of the Medicine Act in 1987, Singapore's initial focus was on evaluation of drugs already approved by other agencies. As of 1998, however, the agency has had the capability to perform first-in-world evaluations and approvals. For the work on scientific reviews HSA has built up a clinical team of: medical doctors, pharmacists, pharmacologist, microbiologist, and biochemist, and a quality assessment team of chemists, biochemists and pharmacists. External evaluators from academia, healthcare institutions and clinical practice are also involved and overseas experts may be engaged if appropriate.

During pre-marketing risk assessment, the depth of the HSA's evaluation depends upon the inherent risk of the product and confidence in prior approval by reference agencies. Consistency of regulatory decisions is ensured through the use of common templates for evaluation reports; peer reviews within evaluation teams; cross-functional reviews; and the opinion of external experts. For all new drugs, advice is sought from the Medicines Advisory Committee.



Since 1987, an **abridged assessment** pathway, has been available, based on the principle of not 're-inventing the wheel' and this accounts for more than 80% of all applications. A **full evaluation** pathway, available since 1998, is used for first-in-world evaluations, with the emphasis on innovative therapies for predominantly regional diseases and those diseases originating in Singapore. Resources are assigned as a priority for full-dossier submissions and approval is accomplished within 12 months.

The **verification pathway**, introduced in 2003, affords a quick review and approval based on approvals by reference agencies. It accounts for 10% of all NDAs and is much shorter (3 to 4 months) than the abbreviated pathway. For all pathways, either the ICH CTD or ASEAN CTD format must be adhered to.

Future opportunities to improve the regulatory system lie in the proposed **Health Products Act** which would consolidate medicines control laws, be more responsive and flexible according to different degrees of risk, define dealers' obligations and establish more appropriate penalties, and offer an opportunity to review the process and licensing requirements. Other initiatives would provide for proactive environmental scanning; foster greater synergy across professional groups; and create better partnerships with local agencies and research institutes, other regulatory agencies, and industry.

SESSION 2: EVIDENCE OF PRIOR REGISTRATION AND THE SCIENTIFIC ASSESSMENT

Colin Vickers, *Head, Worldwide Regulatory Strategy – International & Japan Liaison, Pfizer Ltd, UK*, chaired the second Session of the Workshop, discussed the ways in which evidence of registration in other countries can be used as a cornerstone for the local review and the impact on managing resources.

TAIWAN

Dr Herng-Der Chern, *Executive Director, Center for Drug Evaluation (CDE), Taiwan*, gave an overview, based on his experience in Taiwan, of a system that includes the capacity for in-house scientific assessment but integrates evidence from registration in other countries into a risk-based review.

Agencies face an overwhelming regulatory challenge with limited resources which means prioritising assessments and balancing protection and promotion of public health with making timely regulatory judgments based on a risk-benefit assessment. A study of market roll-out of new medicines between 1996 and 2002 showed a time lag of 30.5 months in Taiwan after first country approval. Being later to market new medicines can, however, reduce the risk of being caught by early withdrawals.

Experience has shown the need for an independent 'Asian voice' in considering the safety and efficacy of new medicines and examples include Iressa™ (gefitinib) which is more effective against lung cancer in Asian populations, lower dose requirements for the statin Crestor™ (rosuvastatin) and the higher risk of Steven-Johnson syndrome in patients carrying the HLA-B*1502 gene, when taking carbamezepine.

Potential solutions for the allocation of limited resources include the concept of 'trust but verify'; the partial recognition of the assessment of other agencies coupled with an in-house capacity for Good Review Practice (GRP) assessments and an external advisory committee. A risk-based classification is made for administrative purposes and to assign the level of assessment, and such a system depends upon partnership with other agencies and international harmonisation. In a system based on trust, sponsors should be held responsible if they conceal important negative information, with spot checks and severe penalties for violation of good practices.

Regulatory science is a relatively new discipline and an in-house review team, rather than relying on outside experts is required to ensure that the elements of GRP are applied:

- The **principles of GRP** include consistency, fair treatment, transparency, communication, efficiency, quality control; data confidentiality, measures against conflict of interest and legal accountability.

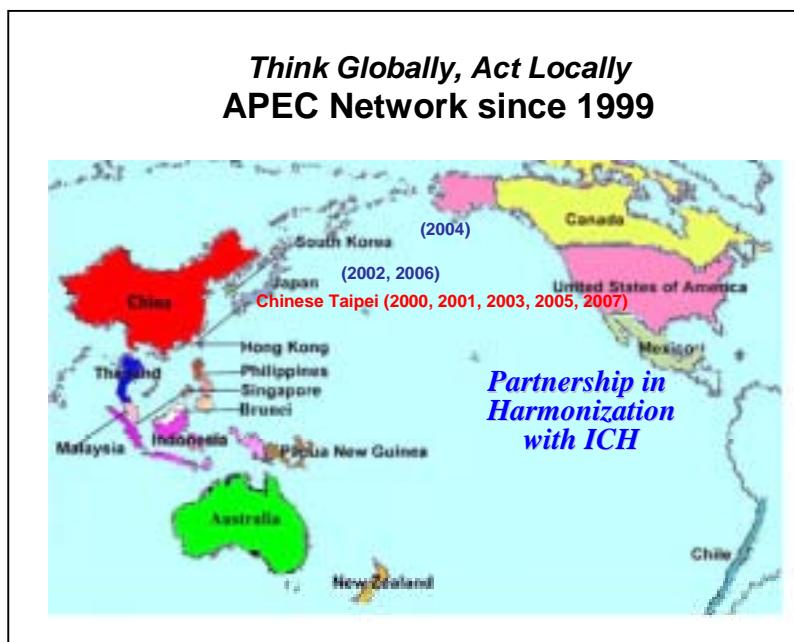
- The **application of GRP** requires: a qualified team of reviewers with a good training program, scientific assessments based on pre-specified guidance, evidence based, risk/benefit evaluations, review templates, consistency and quality control;
- The **process** should be transparent, predictable and timely with good communication, meeting minutes and SOPs.

In Taiwan, the Bureau of Pharmaceutical Affairs (BPA) is the legal regulatory authority with a focus on policy setting, guidance, supervision and compliance. The Center for Drug Evaluation (CDE), established in 1998, is responsible for scientific and technical evaluations and was modelled on the US FDA. Its capacity has grown steadily and in 2007 the scientific and professional staff numbered almost 130, with 21 physicians and 28 PhDs on the staff.

Although there has been a shift from external to internal reviews, the process still relies on pre-registration elsewhere with the CPP as evidence of registration. Legislation on the source of the CPP has not been updated since it was first drafted and, for example does not specifically include the EMEA as a reference source for CPPs. The basic requirements are for one CPP each from Group I countries (France, Germany, Belgium, Switzerland, and Sweden) and Group II countries (USA, Canada, Japan, Australia, and UK). There is some flexibility and a CPP is not required at the time of submission if pivotal clinical trials, involving a substantial proportion of Taiwanese patients as specified in the regulations, are carried out in Taiwan but one or two certificates are still required before approval. For other new chemical entities at least one CPP is required before the application is accepted for review and 2/3 at approval.

In assessing NDAs, CDE considers labelling requirements in countries of approval, and regulatory reports including FDA assessment reports and Advisory Committee minutes, EPARs from EMEA, Pharmaceutical Safety Update Reports (PSURs) and the company's post-marketing risk management plans.

Acceptance of foreign data is based on an evaluation of ethnic sensitivity based on the ICH E5 guideline with bridging studies required unless the product is among the 62% judged as ethnically insensitive.



Exchange of evaluation reports: Efforts to increase the cooperation and partnership between agencies have included discussions on whether a scheme for exchange of evaluation reports, based on the principles of the discontinued PER scheme should be considered. A regional scheme within APEC (see slide) would include both emerging and well established agencies and could cover assessment reports for INDs, NDAs and Bridging Studies. Training programmes on regulatory science and GRP could be a component.

Such a scheme would help build up trust between agencies and

support verification assessments by reducing the need for duplicated reviews. Such a scheme would also provide a platform for involving regulatory agencies and industry in discussions to improve regulatory affairs. Since the possibility of a revived 'PER-style' scheme was discussed at the March 2006 Institute workshop on the Emerging Markets², interest in pursuing this has been shown by CMR, WHO, various regulatory agencies, and pharmaceutical companies.

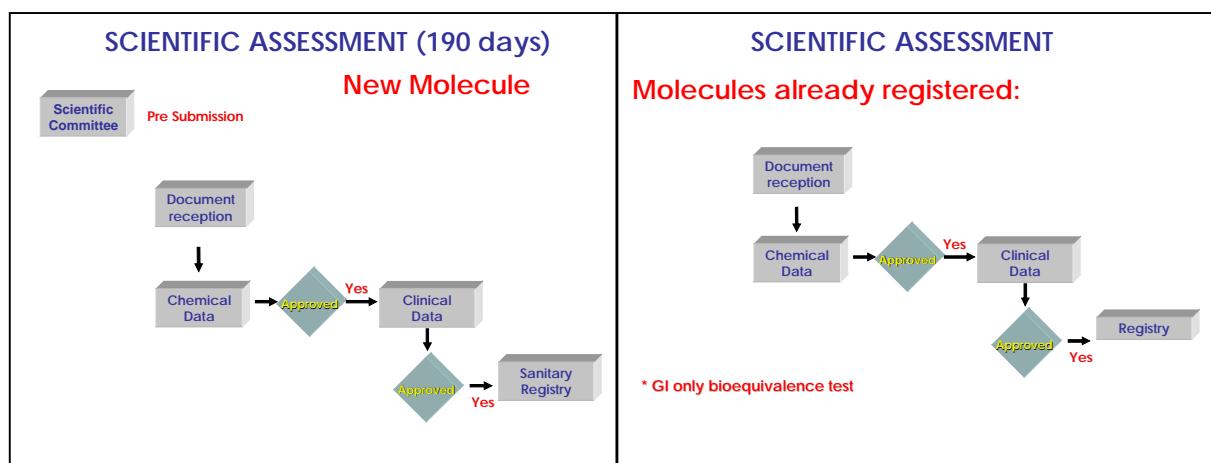
² See inside front cover for reference

MEXICO

Patricia Pineda, Manager on International Affairs on Chemicals and Drugs, Federal Commission for the Protection from Sanitary Risks (COFEPRIS), Mexico, described the regulatory structure and process in Mexico.

COFEPRIS is a relatively new body set up by the Ministry of Health that has financial, technical and financial autonomy. Its objectives include not only protection of public health but also a remit to improve the competitiveness of Mexico's national industries in international markets. COFEPRIS has a broad mandate covering the production, import, export and marketing of a wide range of goods and services from drugs, medical devices, foods and cosmetics to the control of hazardous substances and basic sanitation and environmental health issues.

The agency is headed by a Federal Commissioner and supported by a policy board, scientific board, industry consulting board and advertising consulting board. Different divisions deal with management of sanitary risks, health promotion, regulatory enforcement and analytical control and include the *Commission for Sanitary Authorisation*. This Commission issues licenses; maintains a registry of drugs, medical devices, and pesticides; and issues marketing authorisations.



Mexico has the capability to review new products that are not registered elsewhere. The scientific assessment has a timeframe of 190 days and includes an optional pre-submission step in which companies can meet the Scientific Committee and present a summary of their product and application data in order to obtain guidance on the subsequent submission. The review process is then sequential, with the chemical and pharmaceutical data being reviewed before the clinical data. The pre-submission consultation does not apply to products that are already registered but, otherwise, the review process is essentially similar. Generic products fall into this category and require only bioequivalence data.

For the chemical data, full information with original documentation and validation studies are required except where tests and ingredients fall within pharmacopoeial specifications. The assessment encompasses the manufacturing process, stability, identity, purity, and formula. Once the chemical data are approved, the clinical data are assessed, also from full data and original documents. The clinical assessment addresses adverse effects, the safety index, therapeutic effect, and toxicology. When the clinical data are approved, the submission proceeds to registration.

The assessment of submissions is carried out in-house using only the agency's technical staff. Timing is monitored and the review 'clock' is stopped when requests are made to the sponsor for additional information. Clinical data from foreign laboratories are accepted and Mexican laboratories carrying out trials or other forms of testing must be authorised by the Ministry of Health.

INDUSTRY

Ann Readman, Vice President, International Regulatory Affairs, AstraZeneca UK Ltd, gave an industry viewpoint on making best use of information from registrations in other countries

The Certificate of a Pharmaceutical Product (CPP) remains the primary and most widely used evidence of registration elsewhere. This has been much debated but it is now time for creative and constructive discussions to change and update its utilisation. Industry would support the introduction of an electronic CPP.

One of disadvantages of the current Scheme is that a single CPP tries to serve more than one purpose. It provides evidence of approval, on grounds of safety, quality and efficacy, in the issuing country but it also certifies that the product is manufactured under GMP for that particular country.

Many importing countries require a CPP from the so-called 'country of origin' but the definition of this is not clear or consistent and can be interpreted as the country of primary manufacture or where the packing and quality assurance release is carried out or where the parent company is a legal entity. In some cases the CPP must be from a specified reference country or from a list of countries.

Other means are available to fulfil the CPP's role as evidence of registration elsewhere and these include a copy of the authorisation letter from the source country, or a reference country, provided such letters are consistent in the information that they provide and can be authenticated. Information on registrations is also available from agency websites and it is clear that some countries that insist on a CPP, in practice, also refer to information from websites to support their evaluation.

Flexibility and pragmatism are qualities that industry seeks from agencies on the question of evidence for prior authorisation. Experience has been positive in cases of products for unmet medical need when discretion has been exercised over, for example, the country that supplies the CPP and acceptance of letters of approval instead of a CPP and whether the CPP must be available at the time of submission or just prior to approval.

Another area where companies would like a more flexible and realistic attitude is in requiring evidence of the marketing status in the country that issues the CPP. This can cause unnecessary delays and work for both agencies and industry and the information is not relevant to the assessment of safety, quality and efficacy. There are many valid reasons why a product might not be marketed at the time the certificate is issued.

Trusted sources of evidence: Agencies can and should trust CPPs from known and reliable sources and industry would like authorities to have a common list of accepted *Competent Authorities* such as that published by WHO (See box). Letters of approval from such agencies could be trusted and are easily verified, especially with information being published on their websites. In addition, industry believes that an agency performing a full assessment of quality, safety and efficacy should not also require a CPP in order to grant approval

Industry questions whether, in an age of increasing transparency, the formal legalisation of documents through Embassies and Consulates is still necessary, especially when dealing with recognised reference agencies.

WHO list of 'Certified Authorities'

In the discussion, Dr Lembit, WHO, corrected a widely held, but mistaken, belief that WHO certifies the competence of the authorities that are listed as eligible to issue Certificates under the WHO Certification Scheme. In the Guidelines on the Scheme, WHO sets out the criteria that authorities must meet in order to issue CPPs (including an effective national licensing and enforceable GMP requirements) but agencies are *self-certifying*. The guidelines state 'Each Member State assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites'.

http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html
Follow the link to 'eligibility for participation'.

WORLD HEALTH ORGANISATION

Dr Lembit Rägo, Coordinator Quality Assurance and Safety of Medicines, WHO, summarised his organisation's perspective on best use of national resources in the assessment and inspection of innovative products.

In theory, all national regulators could re-assess and inspect all new products that enter their markets but, in practice, very few of the 193 member states of WHO have the resources to do so and nor would this be optimal use of those resources. Repetitive assessments and inspections only give added value if the previous assessment has been based on a different – and lower - set of standards or has missed important issues due to different qualifications or views. Repetitive assessment is not usually useful if the same standards have been used or if the regulatory agency does not have an assessment capacity equal to that of the previous assessors.

Regulatory science is built on the principles of risk assessment, management and communication and agencies should follow the same principles in the review of new medicines: assess, manage, and communicate. They should consider different models that have been used in the past and determine which ones work best for that agency.

Confidence-building in the scientific assessments carried out by other parties is one of the keys to success but this must be a two-way street. Trying to build confidence based on 'one way traffic' is likely to lead to failure.

Best use of resources: All agencies believe that they are under-resourced from the US FDA to the agencies that have 'one-and-a-half assessors'. Regulators must therefore determine how they can best contribute to the patients in their country with the available resources (see slide). They should focus on measures that give added value, for example, the national labelling and how it has been translated or the impact of local medical practice, and concentrate on high-risk areas and products. Pragmatism is necessary in determining the information that is needed and many agencies are already following these recommendations.

How can regulators best contribute to the public health with the resources they have?

- Ask the question how YOU can best contribute to the patients in your country setting with the resources you have
- Avoid doing things that do not give added value, concentrate on things that do give added value
- Concentrate on high risk areas/products
- Be pragmatic – Nice to know – forget it, need to know – get it! And learn making difference between the two
- A lot of this is already happening



How to go forward: Issues for the future should not only focus on marketing authorisations. They include communication about variations and evolving post-market safety issues and the role of 'second reviewers' in pharmacovigilance for products that are marketed globally. Local safety issues might be slightly different and disease patterns, traditional remedies and co-morbidity may all play a part.

Much has been said about needs for improvement in the Certification Scheme but the CPP has served a useful purpose and is probably 'too young to die', although changes are needed as it has, undoubtedly, been misused, mismanaged and misinterpreted on occasions. Greater transparency might be one answer with CPPs and inspection reports being made available to all agencies, either through protected websites or in the public domain.

With regard to the scientific standards for review, the ICH Global Cooperation Group (GCG) has an important role in helping agencies understand the use and relevance of ICH Guidelines. Wider acceptance of the ICH Common Technical Document (CTD) would also assist efficiency in handling global applications. Industry also has a role in allowing agencies to share information on applications and examples from the past include the PER Scheme for exchanging regulatory assessments.

Well-resourced agencies should seek ways to communicate with and help those that are less well-resourced. Examples include international staff exchange programmes, the designation of a 'rotational post' for less-resourced regulators and joint inspection programs.

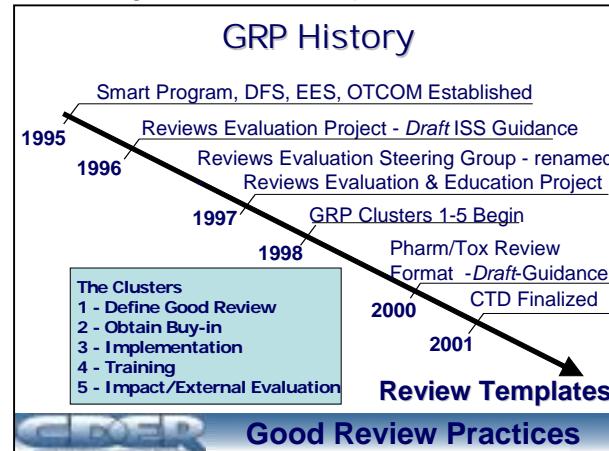
SESSION 3: QUALITY MEASURES AND PROJECT MANAGEMENT IN EMERGING MARKETS

This session was chaired by **Dr Justina Molzon**, Associate Director, International Programs, CDER, FDA, USA, and looked at the ways in which authorities are building quality into their review and the project management practices that are being adopted.

Introducing the Session, Dr Molzon provided a brief update on the status of Good Review Practices (GRP) as adopted by CDER, FDA. GRPs were established to bring about the continuous enhancement of review practices through refinement, re-design and overall improvement.

The GRP project started in 1995 with the Smart Program concerned primarily with training and the next milestone was the drafting of guidance for the format and consistency of the *Integrated Summary of Safety* (ISS). Five 'clusters' were set up in 1998 (see slide) to move the project forward but a major factor was the adoption of the ICH *Common Technical Document* (CTD) in 2001 that resulted in submissions being received in a consistent format. Review templates could then be developed and GRP documentation is now published on the CDER website:

<http://www.fda.gov/cder/other/grp.htm>



The fundamental values of CDER's GRP are quality, efficiency, clarity, transparency and consistency. But GRPs also provide an overall quality systems (QS) approach to product review. CDER's QS approach is:

Say what you do → Do what you say → Prove it → Improve it

which translates into the QS approach to GRPs as:

Develop GRP → Implement → Mentor and train staff → Evaluate or re-evaluate

In summary, CDER's Good Review Practices: Provide a more consistent approach to the review and approval of new products; Specify process, format and content of a review; Standardise reviews and review management; Train staff on the review process; Inform industry and the public of CDER's internal review best practices and processes; and Provide an overall quality systems approach to product review

INSTITUTE STUDY

Professor Stuart Walker, Vice President & Founder Institute for Regulatory Science, gave a *Comparative Review of the Quality Measures being applied to the Regulatory Review in the Emerging Markets*. Please refer to Annex 3 of this report for background information on the Institute Study to which this presentation referred.

The section of the Institute study on 'Quality' sought to determine how the authorities are building quality into their regulatory processes and the practices that are being adopted and to identify any specific developments and differences in the way in which quality measures are being applied.

The study also looked at how the authorities are periodically evaluating quality in the review process and the activities being undertaken to improve communication and transparency of decision-making, as well as the main factors that are driving authorities to improve quality.

'Quality' is a notoriously difficult concept to define but an earlier and on-going study among established regulatory agencies³ identified eight key measures that are essential for Good Regulatory Review Practices (GRP). In the Institute Study these eight components of a quality review were defined as set out in the table below, and as the 'baseline' for obtaining comparative data from the agencies in the study.

Components of a Quality Review

1. **Key quality documentation:** regularly updated and comprehensive quality policies, standard operating procedures and assessment templates.
2. **Professional development** of assessors and retaining of staff: adequate incentives to competent staff, and regular training of assessors that focuses on, e.g. improved practices; scientific and technological advancements; knowledge and skills transfer.
3. **Built-in quality controls:** such as systematic management checks, structured approach to decision-making and robust internal tracking systems.
4. **Internal reviews:** a structured and integrated peer review system, as well as expert reviews by independent advisory committees.
5. **Benchmarking and key performance indicators:** such as regular use of quantitative indicators on processing times; response times; frequency and number of withdrawals; as well as the carrying out of benchmarking exercises that compare processes or outcomes.
6. **Continual improvement activities:** conducting internal quality audits, self-assessments, analyses of feedback from stakeholders, post-approval analysis with other authorities and industry, management reviews, and using the results to take corrective action or introduce improvements to the review process and decision-making.
7. **An established setup and process** that allows regular contact with industry: for example, to discuss development and review plans, clarify statutory requirements, provide scientific and regulatory advice, inform the applicant on how the review is progressing, and develop 'partnerships' and synergies between the two parties.
8. **A transparent system** that provides important review information to the public: for example open public hearings of advisory committee meetings, or the publication of the summary basis of approval and assessments following approval.

Motivation: When twelve agencies were given a list of seven possible reasons for introducing quality measures and asked to select the three most important the first selection was 'to ensure consistency' (11/12) the second 'to ensure efficiency' (9/12) and the third 'to minimise errors' (6/12).

Quality measures in place

Agencies were given a list of quality measures and asked whether they were currently implemented or planned for the near future. It was noted that the agencies are at different stages of development and also that they were undergoing rapid change, even in the two years since the study was initiated.

Looking at the overall approach to **quality management** eight authorities (Argentina, Brazil, Mexico, India, Indonesia, Malaysia, South Korea and Taiwan) have an internal quality policy. Indonesia, South Korea and Taiwan have a member of staff responsible for the development of quality and good review practices and four (Argentina, Brazil, India and Malaysia) stated that they have a department for assessing and ensuring quality, but there are differences in the structure and resources allocated to these internal units.

With respect to **quality documentation** ten authorities use SOPs for the guidance of scientific assessors: Argentina, Brazil, Mexico, India, Indonesia, Malaysia, Singapore, South Africa, South Korea and Taiwan.

Eight authorities use assessment templates for reports on the scientific review of a new active substance: Argentina, Brazil, Indonesia, Malaysia Singapore, South Africa, South Korea and Taiwan. These templates set out the content and format of written reports on scientific reviews. Egypt and Saudi Arabia indicated that they intend to introduce both SOP and assessment templates within the next two years.

³ The CMR International Institute Benchmarking Study, initiated in 1998, collects data on the regulatory review processes in USA, Europe (EU), Canada, Australia and Switzerland.

Four authorities (Indonesia, Mexico, South Korea and Taiwan) indicated that they have implemented a GRP system and Malaysia has all the components of a GRP system. There can be, however, considerable differences in the extent of development of these systems. Argentina, Egypt, India, Singapore, and South Africa reported that they plan to introduce a GRP system in the near future.

Continuous improvement measures included collecting feedback from stakeholders following a review, which is carried out by all twelve agencies studied, and reviewing feedback from the assessors themselves (eleven agencies). Ten agencies had internal tracking systems to monitor applications and review progress and eight reported that they had formal training programmes. External quality audits were relatively infrequent (3/10) and internal audits were even more infrequent (3/12).

Communication, transparency, openness

Companies place great emphasis on the advantages of working with an agency that operates in an open and transparent manner but there is a perception that it does not always work both ways.

Nonetheless, nine out of eleven agencies that responded assigned a high priority to being open and transparent. (Information was not available from Brazil). When asked about the specific benefits 10 out of 11 agreed that it increased confidence in the system, 9 felt that it helped provide assurances on safety safeguards and 7 believed it led to better staff morale and performance. Other related attributes are shown in the slide

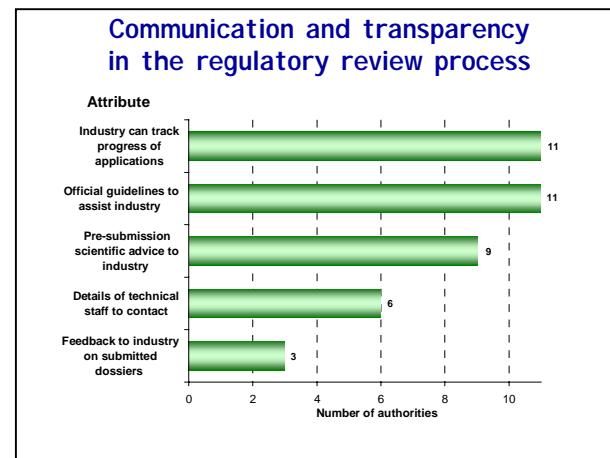
There was general agreement that authorities can enhance their standing with the public, health professionals and industry, by allocating time and resources to provide information on their activities and decisions in an open and transparent manner

Conclusions

Quality Measures: Most authorities in the emerging markets have a range of quality systems and measures (SOP's, Assessment Templates) but they are at different stages in their development and maturity. The least number of implemented measures were found in the Middle-East countries in the study (Saudi Arabia and Egypt)

Continuous Improvement Initiatives: Many agencies have focussed on improving their assessment of feedback from stakeholders and reviewers as well as establishing tracking systems, although few have either internal or external quality audits

Good Regulatory Review Practice: The importance of establishing and implementing a GRP system is well understood although few agencies have achieved this to date. Several, however, are planning this within the next two years although the level of detail and value has yet to be assessed.



CONFIDENCE IN A QUALITY REVIEW

Alistair Davidson, VP, International Regulatory Affairs, GlaxoSmithKline, UK, gave a company perspective on the key elements for a quality review.

Firstly, behind all the paperwork and process the primary consideration for both companies and agencies is to ensure that the ultimate 'real world' objective is not lost and the review has been performed with the end user – the patient – in mind.

Recognising that each agency is different in terms of resources and structure there are nonetheless elements that are common to a quality review. These include:

Predictability and clarity of process allow companies to understand time lines and be able to plan accordingly. The steps in the process and expected time intervals need to be known, taking account of the different types of products (new chemical entities, generics, variations and OTC products etc) and including the procedures available in the event of a rejection.

Although processes are governed by laws, regulations and written procedures, there should, nonetheless, be the flexibility for regulators to be allowed to exercise good judgement.

Resources to manage the process must be adequate in terms of quality and quantity and this applies equally to external experts and internal staffing and the systems that support them. External experts must have the right qualifications, be adequately reimbursed and understand the implications of conflict of interests and the importance of confidentiality. Internal staff numbers must be adequate to meet process targets and individuals must have appropriate qualifications, training, experience and motivation.

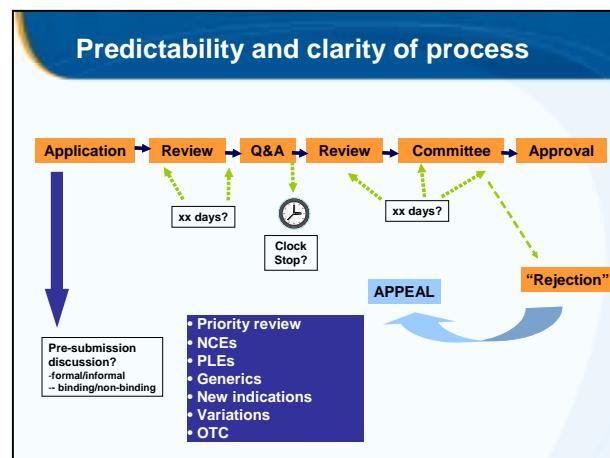
Communication with the agency before during and after the review process, whether by telephone, E-mails or face-to-face meetings, is an important element for companies. It is recognised that working practices vary between agencies and it is important that they are clear. Companies are seeking flexibility but have a responsibility not to overburden the system and impair its efficiency.

Cost/value: Registration fees are recognised as an established means of funding regulatory agencies and companies are prepared to pay 'a reasonable fee for a reasonable level of service' but fee levels should be appropriate to type of assessment and the work that needs to be done. Where possible, fees should be used for agency maintenance and development and should not, for example, be absorbed into central government finances. Information on fees and their collection and use should be transparent and reported publicly each year.

Handling of issues that are product-related and unexpected involves both agencies and companies and can arise during and outside the review process. Companies have developed working practices for 'crisis management' and business continuity if serious incidents occur that, for example, interrupt production and supply. Agencies may be less prepared to deal with urgent situations but need contingency plans that ensure that the facts are established and confidentiality is maintained until public release of information is appropriate in the interest of patient safety.

Reporting and measuring: The end product of the review process is the licence or authorisation which must be clear and unambiguous with and post-approval commitments clearly specified. Subsequent changes should be communicated as appropriate, e.g., safety updates to the label of the original product must be reported to relevant generic licence-holders.

Agencies should also be accountable through the annual publication of metrics on applications received, granted, refused, cancelled etc., and whether performance targets were achieved.



Future development of quality reviews require agencies to examine their own performance critically and base their plans for resources and targets on robust predictions of future demands and products in the pipeline. Industry must be involved and asked to cooperate in such planning

Building quality into the review process

Two discussants gave their views on the *Importance of building quality into the review process* from the perspective of a developed and a 'developing' agency:

AUSTRALIA

Dr Jason Ferla, *Drug Safety and Evaluation Branch, Therapeutic Goods Administration (TGA), Australia*, discussed the topic of quality in the review process from the perspective of a well-established agency with some 500 employees for the Australian population of some 21 million. The agency, which operates on a basis of 100% cost-recovery from fees, regulates all types of human medicines, medical devices and blood and tissue products and its areas of responsibility cover the whole product life-cycle from clinical trials and pre-marketing assessment to post-marketing extensions and surveillance.

Quality is considered important in order to provide a framework for evidence-based decision-making in the approval of safe, effective and high-quality goods. It is crucial in building confidence in the regulatory system and promoting a better understanding of the value of pharmaceuticals. Operating a system that provides fairness and 'natural justice' for industry also encourages a healthy environment for the development of new medicines.

To ensure quality in the review process, the TGA provides for consistency in decision-making, controlling risk, controls in the review process, competence of evaluators and advisors, continuous improvement, and communication and transparency.

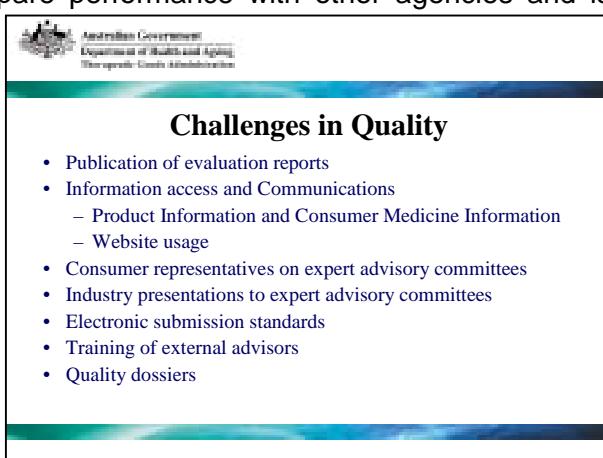
For **consistency and risk control**, the agency uses checklists, templates, SOPs, risk management plans, and lifecycle management.

Controls in the review process include: review and feedback on evaluation reports by senior officers; standardisation of elements in the review process (e.g., guidelines, dossier format); and independent review by an external Expert Advisory committee and internal Peer Review group.

Programs exist for the **professional development** of both internal and external evaluators and advisors through training and continuing education programmes.

The TGA strives for **continuous improvement** through monitoring and updating review processes to improve and update SOPs. Timelines and clock stops need to be closely monitored as the review target of 255 working days is written into the legislation. TGA participates in the CMR International Institute benchmarking study to compare performance with other agencies and is subject to external audits within the Australian government system. International activities and interaction with other agencies, particularly in SE Asia are also important.

Communication and transparency with industry is established through meetings and interaction with individual companies and there is an extensive consultation process on proposed regulatory changes. Information to the public and health professionals is mainly through the agency website and written communications sent directly to practitioners.



Challenges in Quality

- Publication of evaluation reports
- Information access and Communications
 - Product Information and Consumer Medicine Information
 - Website usage
- Consumer representatives on expert advisory committees
- Industry presentations to expert advisory committees
- Electronic submission standards
- Training of external advisors
- Quality dossiers

Current and future challenges to improve quality (see slide) lie mainly in extending the information available via the website (e.g., to include evaluation reports) and integrating consumer representation and industry presentations into the committee process. Other projects include adoption of the electronic CTD and enhancing the training of external advisors. The quality of dossiers has improved, although further work is needed.

MALAYSIA

Noorizam Ibrahim, *Head of New Chemical Entity Section, National Pharmaceutical Control Bureau (NPCB), Malaysia*, discussed the situation in her agency, presenting a brief profile of Malaysia and summarising the role of medicines as an instrument of public health, the nature of regulatory control, and the vision, mission, objectives, and strategies of the NPCB.

Quality Attributes In Review Process

- Confidence of reviewers, sponsors and public in the regulatory decisions made
- Efficiency and consistency in process
- Timely delivery of new drugs without compromise on safety, quality and efficacy
- High quality reviews based on in depth, science based approach
- High quality clinical trial data for assessment of safety and effectiveness of the new drug
- Good collaboration with sponsors to ensure information submitted adequately address the drugs quality, safety and efficacy

Malaysia has a population of 26.9 million in a land area of some 330,000 sq. km. The Control of Drugs and cosmetics Regulations Act 1984 empowers the Drug Control Authority (DCA) to implement drug regulation and the NPCB of the Ministry of Health is entrusted to carry out regulatory activities.

The attributes required for a quality review have been defined (see slide) and it is the responsibility of NPCB to implement the appropriate procedures to address these.

The key to upholding **confidence in regulatory decisions** lies in a sound, transparent and systematic regulatory system backed by a comprehensive legal framework. The benefits of establishing an open and transparent relationship between regulators and industry is acknowledged and open dialogue are encouraged. NPCB is particularly concerned with maintaining staff integrity and awareness of the need for confidentiality. Transparency is achieved by making available, in the public domain, comprehensive guidance documents, technical guidelines, information on fees requirement and other relevant documents.

Ensuring a **timely review process** is established through setting realistic targets for review times, with priority for urgently needed products for unmet medical needs. Efficiency is, however, dependent on the quality of submissions and a complete, well organised file will expedite the review process.

To support an **efficient and effective** review process the agency requires data submission in a standard format and has adopted the ASEAN Common Technical Document (ACTD). Standard templates are used for reporting the scientific review in order to ensure a comprehensive and consistent approach and internal guidance and policy documents are available.

Emphasis is placed on **education and training** of reviewers with requirements for a minimum basic degree and the provision of on-the-job training as well as continuous professional development programmes.

In the face of a challenging regulatory environment, the NPCB is committed to ensuring timely delivery of safe, high-quality, effective drugs to the public. A comprehensive regulatory system is in place, and continuous quality-improvement initiatives have been implemented to upgrade the infrastructure and encourage better resource management. Maintaining internal and external communication and dialogue with other Drug Regulatory Authorities (DRAs) and industry is a key component and financial resources are sought to meet training and international obligations

Adherence to Good Regulatory Practices in the midst of high workload and pressure is one of the challenges as well as managing and measuring quality performance through audits and increased transparency and maintaining flexibility to adapt and react to public health needs. International benchmarking is seen as the way forward, with adherence to international codes of good practice (through GMP, GCP, GLP, etc.) and strategic partnership with industry, academia, consumers and health professionals.

The Malaysian regulatory agency has achieved international recognition as a WHO Collaborating Centre for Regulatory Control of Pharmaceuticals (1996) and through membership of PIC/S in 2002.

INDUSTRY

Dr Matthias Hoepfner, Vice President, Head of GRA International, Bayer Healthcare AG, Germany, gave an industry viewpoint on the ways in which companies could help agencies to conduct a quality review.

Much depends on early communication and companies' support for a quality review starts with early, initial communications about major upcoming submissions and by requesting pre-submission meetings to discuss the development rationale along with a high-level overview of the dossier content and technical questions.

Companies can help regulatory agencies by giving careful consideration to four aspects of the submission and review process (see slide):

Applicants can support a quality review

- by communicating upfront with health authority about major upcoming submissions („pre-submission meeting“)
 - Development rationale
 - High level overview on Dossier contents
 - Technical questions
- by giving careful consideration to
 - Dossier Quality
 - Dossier Size
 - Quality of Answers to Questions
 - Speed of Providing Responses



Dossier quality: It is common practice for the core documentation of a global application to be in a single language (usually English) and the accuracy of translations into the local language is critical.

The need to produce applications in diverse national formats is inefficient and leads to a lack of consistency. Adoption of the ICH CTD as a common format for dossiers means that submissions to different agencies are comparable and that reviews are carried out on the same basis. Schemes for the exchange of assessment reports would depend on such a premise.

The CTD format does not preclude the inclusion of region- or country-specific documentation. An

important feature, however, is the inclusion of high quality Summaries and Overviews that cover the totality of the data in the full submission and provide a critical evaluation of both benefits and risks.

In compiling the content of a dossier it is important to ensure that cross references from summaries to the full data are clearly highlighted and easy to find and that all statements in the label are supported by data.

The **Dossier size** for an application compiled according to the CTD is extremely large for a NCE application and the review of the entirety of the data requires well staffed and well organised review teams. Many Health Authorities could benefit from receiving, initially, an abbreviated version of the CTD that consists of high quality Summaries and Overviews supported by the essential additional information. Companies must then be prepared to make all detailed documentation available upon request within a short time.

The **Quality of answers** to questions needs special attention and companies should develop processes for providing complete responses to all requests from the regulatory authority, in an easy-to-read, consolidated format, and in a timely manner.

The **Speed of providing responses** will obviously influence the overall review time and companies should ensure that their local representatives have the information and resources to deal with minor telephone enquiries that require an immediate response. More detailed requests need ground rules to be established and followed within the company. Transparency on when responses can be expected will help the authority to manage resources effectively but companies also need to know, from the agency, the stage (timepoint in the review) at which questions might be expected and the response time allowed.

Finally, a quality review is not an end in itself but a means of arriving at a quality decision. The common goal of both industry and agencies is the timely availability of high quality new medicines to healthcare professionals for the sake of the patient.

BENCHMARKING

During the discussion following this section the question of extending the CMR International Institute Benchmarking Study to Emerging Market countries was raised. The Institute study has been following the approval of applications for new active substances and major line extensions by FDA, EMEA, TGA, Health Canada and Swissmedic for over 10 years and monitoring not only overall approval times but also the time spent by applications at different stages in the review. Inclusion of other agencies in a similar study would be dependent on the availability of suitable application tracking systems and the agency's willingness to retrieve and share data.

The methodology for the Institute project has been published in the DIA Journal⁴ and Professor Stuart Walker, *Institute for Regulatory Science*, confirmed that the Institute would welcome proposals from other agencies to be included in a similar Benchmarking project.

PROJECT MANAGEMENT AND APPLICATION TRACKING SYSTEMS

Caroline Vanneste, *Project Manager, Good Review Practices, Therapeutic Products Directorate, Health Canada*, described the philosophy behind the project management procedures adopted in by her agency and the processes implemented to address these.

'A good review process incorporates timeliness, predictability, consistency, and high quality. Project management and tracking systems are two tools that can assist in achieving a good review process'.

Whilst a good review process is the goal of every agency there is not yet a common definition. Within Health Canada, Good Review Practices are defined as 'review standards (such as standard operating procedures and templates) and related initiatives (such as reviewer manuals and training programs) designed to ensure the timeliness, predictability, consistency, and high quality of reviews and review reports'. Implementation should lead to a Good Review Process which is 'a procedural system that results in timely, predictable, consistent, and high quality reviews and review reports'.

Project Management

Project management is 'the discipline of organising and managing resources (e.g., people) in such a way that the project is completed within defined scope, quality, time, and cost restraints'.

⁴ A Comparison of the Drug Review Process at Five International Regulatory Agencies, Drug Information Journal 2007, Volume 41 pp 291-308.

In regulatory project management, the submission is the project and the objective is that they 'will be managed with the necessary planning, coordination, and management of activities to oversee completion of reviews within performance targets'.

The benefits of implementing Regulatory Project Management have been to facilitate a team approach to individual reviews, to assist planning and to provide better communication with the company and with internal, senior management.

Project managers manage the submission, not the people. Thus they are not involved in resource management, selection of review team members, setting timelines or dealing with budgetary issues.

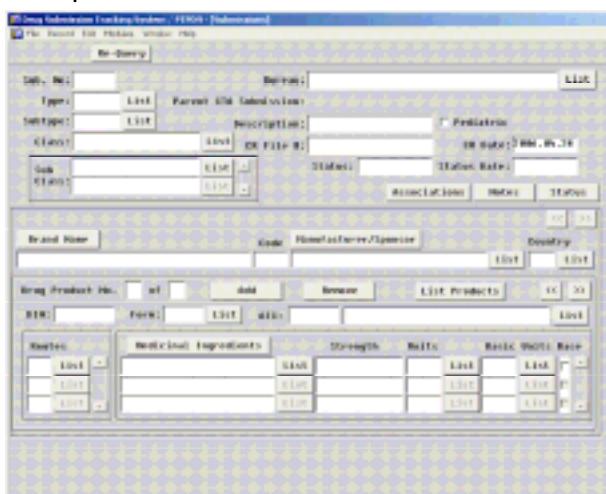
Tracking Systems

Health Canada has introduced four monitoring systems to track quality.

The **Drug Submission Tracking System (DSTS)** is the main one of these and holds information on all applications for marketing authorisations and their progress. The data is web-based and relevant information can be accessed on a confidential, secure link by application sponsors.

The DSTS information enables the publication of quarterly and annual reports drug submission performance results which are in the public domain, via the website.

The **Product Database** is a searchable, web-based database of products approved for use in Canada that is open to the public. It provides basic information on dosage forms, strengths, and therapeutic classes and includes both marketed and discontinued drugs.



The difference in extent of data in the two systems is contrasted in the illustrations.

There is also an internal The fourth and most recent system is for **Tracking Review Quality** and one function is to ensure that SOPs and review templates are being used appropriately. Meetings with companies have been held under the process to obtain feedback on review processes as part of continued improvement.

INDUSTRY VIEWPOINT

Jennifer Chung, Senior Manager and Liaison, Global Regulatory Affairs, Schering-Plough Corporation, USA, gave a presentation on behalf of the scheduled speaker, **Mary Jane Nehring**, Executive Director, Global Regulatory Affairs, Schering-Plough Corporation, USA, in which she put forward a company viewpoint on the importance of tracking systems and project management within regulatory agencies.

In terms of the overall review process Health Authorities should publish information on the review process that clearly identifies the different phases of review and the official, target review times for different types of application (NCE, line extension, etc.). Dates for important meetings (advisory committees, expert meetings, etc.) should be readily available.

For individual submissions there should, ideally, be an electronic tracking system which provides, preferably via a secure website link, accurate information on the status of the review.

Having such information available is of mutual benefit to the agency and industry in that it allows the local company affiliates to partner with the Health Authority in planning the workload for the review of a submission. One example is to be able to anticipate when meetings between reviewers and the parent company may be necessary, another is to ensure that key documents, such as the CPP are available in a timely manner and do not delay the review.

From a company perspective, more accurate information on the progress and timing of a review allows forward planning for the launch in order to ensure, for example, that product supplies are available with the appropriate labeling translated for the local market.

Similar factors apply when looking at the implications for companies of accurate information when integrating the local review process into the global development and roll-out of a product (see box).

Global Perspective

Clear communication by authorities, of review targets are required to plan for:

- Responding to health authority questions
- Ensure project team availability
- Especially important when responding to many health authorities at once

Proactively plan for required inspections

- Avoid hosting multiple inspections at the same time

Arrange for product samples to be delivered in time for analysis

- Timing of product launches-appropriate product supply

Industry's perception of the importance of project management to Health Authorities is in the ability to track all aspects of an application's progress, including the review by outside experts and to establish a single contact point for interaction with the sponsor.

International Cooperation and Initiatives

WORLD HEALTH ORGANIZATION

Mrs Malebona Precious Matsoso, Director, Department of Technical Cooperation for Essential Drugs and Traditional Medicines⁵, WHO, rounded off this section of the Workshop with a presentation on initiatives led by WHO to assist regulatory agencies, at all stages of development, improve the efficiency with which they review and approve new medicines.

⁵ Mrs Matsoso has also been appointed as Director PHI (Public Health, Innovation and Intellectual Property) within the Organization

Initially, a survey had been carried out in Sub-Saharan Africa among pharmaceutical manufacturers (generic and innovative) and regulatory authorities that had *inter alia* identified the perceived problems encountered by industry and by regulators, in the authorisation of new products. These, to a large extent, reflected issues raised in the current Workshop (see Table).

Problems identified in the survey	
<p>Industry</p> <p>Long timelines</p> <p>Lack of skills and expertise in agencies</p> <p>Lack of communication</p> <p>Absence of guidelines</p> <p>Lack of consultative meetings</p> <p>Tracking of applications unsatisfactory</p> <p>Resource and capacity constraints of the agencies</p> <p>Inflexibility of agency procedures</p> <p>Cumbersome and differing requirements</p> <p>Lengthy and unstructured registration procedures</p> <p>Non-acceptance or acknowledgements of approvals in well-established regulatory authorities.</p> <p>Absence of guidelines for the management of post-registration technical amendments in some countries.</p>	<p>Regulators</p> <p>No specific requirements for fixed dose combinations (FDCs), vaccines, new dosage forms</p> <p>Some agencies require certain regulatory data that others do not</p> <p>Limited capacity has resulted in some requirements not being implemented</p> <p>Most rely on WHO prequalification for both drugs and vaccines</p> <p>Not enough evaluators with required expertise</p> <p>Poor responses to enquiries or requests for information from sponsors</p> <p>Inability to track a dossier to determine status of the application.</p> <p>Poor quality of submissions</p> <p>Insufficient data</p> <p>Unsubstantiated claims for products</p>

The outcome and recommendations from the meeting have led to WHO adopting an initiative to develop a **Model Registration Package** that would assist agencies with limited resources to utilise approval by the more established authorities, US FDA, EMEA etc., or jointly review new products with the support of well-established agencies. It was emphasised, however, that individual authorities are obliged to give specific approvals for their countries and not simply adopt the decisions of other agencies.

It was noted that some of the mature regulatory authorities publish information on the basis of their decisions but these are in different formats and other agencies often spend time and resources trying to find the relevant information to support their internal decision-making process.

Technical Package

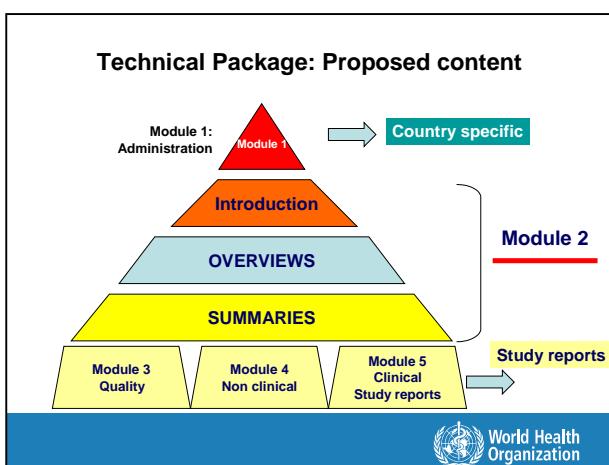
The concept of a 'technical package' is that it should be a document that:

- Is developed by one regulatory authority for a specific pharmaceutical product, containing the scientific information, discussions and conclusions reached at the end of the evaluation process on the quality, safety and efficacy;
- Results from the documentation submitted by applicant, the assessment performed by the RA and subsequent discussions.
- Is made available to other regulatory authorities to support or facilitate their own decision making process.

The objective is to organise and improve the flow of technical, scientific and regulatory information among regulatory authorities in order to accelerate the process of registration and facilitate the access to new drugs.

The proposed structure of the *Technical Package* would be modelled on the ICH Common Technical document (CTD) as shown in the slide.

The issues to be addressed include: the need to rework reports from established agencies that are not in line with the proposed package; the need for confidentiality agreements involving the recipient countries; the question of a secured, web-based 'place to share' from which the package could be accessed by authorised agencies; the challenges of language and translation.



Current Situation

The publicly available information from Health Canada (Summary basis for Decision), EMEA (EPARs) FDA (approval History, DRUG@FDA) was reviewed and also WHO Public Assessment Reports (WHOPAR) and Public Inspection Reports (WHOPIR).

Guidance on the proposed report format has been drafted in English and in French and experts from WHO members states have been consulted. An Inter-regional meeting involved 60 experts from 40 countries in all six WHO regions and this was followed by three much smaller consultations in 2007.

The European Commission has supported a field testing exercise among seven participating countries on one drug application provided by DNDI⁶ and a second from WHO's Tropical Disease Research programme (TDR). Other field testing is planned for 2008 and WHO's approach will be to encourage consolidating and integration of the package into drug assessment, at a regional level.

In summary, the WHO survey has highlighted opportunities to address the problems identified in the responses. Participating countries are serving as resources for regional blocs of nations, supported by well-resourced agencies. WHO is encouraging exchange activities between well-resourced agencies and developing agencies in the first wave of countries.

SESSION 4: CLINICAL TRIAL APPROVALS: PROCESS, TIMELINES AND ISSUES

Professor Stuart Walker, Vice President and Founder of the Institute, chaired the final session due to an unavoidable late cancellation by **Professor Sir Alasdair Breckenridge**, Chairman of the Medicines and Healthcare Products Regulatory Agency (MHRA), UK.

CMR INTERNATIONAL INSTITUTE STUDY

Jennifer Collins, Project Manager, CMR International Institute for Regulatory Science, presented a cross-agency comparison of information collected from regulatory agencies on clinical trial authorisation procedures under the Institute Study on the Emerging Markets (see Annex 3).

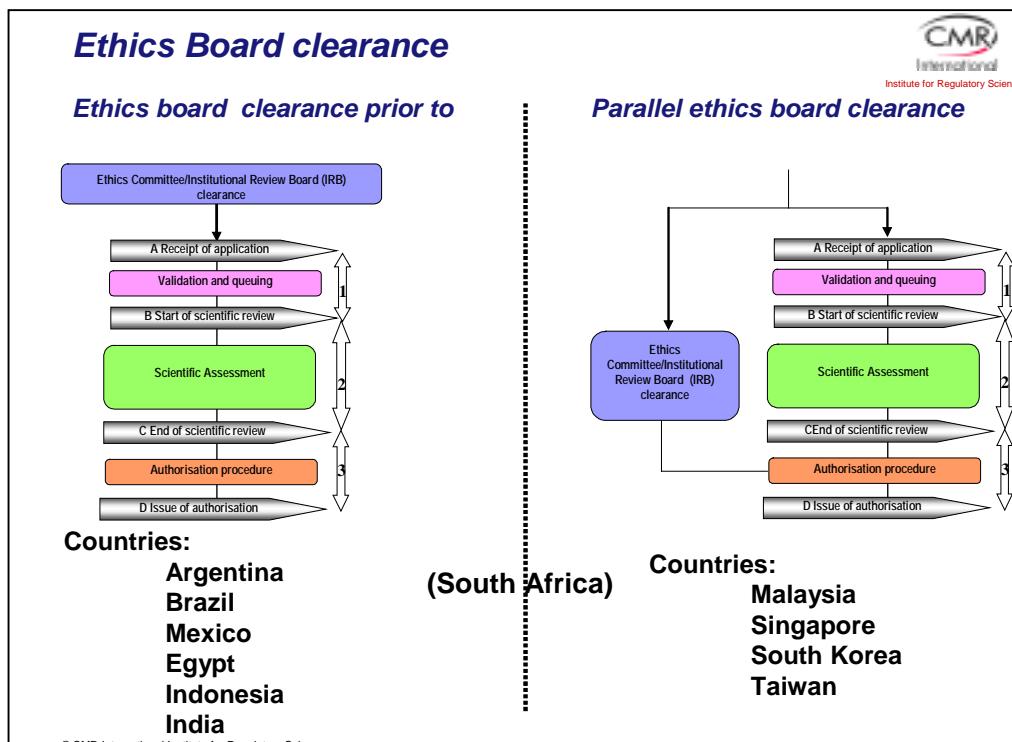
Over the last decade there has been a significant growth in patient recruitment from 'non-core' countries⁷ to participate in global clinical development programmes. By 2005 just over 50% of patients came from non-core countries, including Latin America and Asia Pacific⁸.

In the Institute study, data on clinical trial applications was collected from both agencies and companies and covered process models, use of ethics committees, data requirements, target timelines and actual approval times.

⁶ Drugs for Neglected Diseases Initiative (DNDI), an independent, not-for-profit drug development initiative founded in 2003 (www.dndi.org)

⁷ Core countries are defined as EU countries - France, Germany, Italy, Spain, and the UK, North America - Canada and USA, and Japan

⁸ CMR International 2007 Pharmaceutical R&D Factbook



Ethics Board clearance

All the countries in the study required clearance by Ethics Boards before trials could take place but the timing of such clearance in relation to the authority review differed. The two main models are shown in the slide with prior ethics approval being required in Argentina, Brazil, Mexico, Egypt, Indonesia and India while the Authority and Ethics Boards work in parallel in Malaysia, Singapore, South Korea and Taiwan. In South Africa, the requirements call for prior ethics approval but, in practice, there is some flexibility and applications can be processed in parallel.

There is a third option where ethics review takes place after the trial has been approved by the authority but this model was only found in China. Saudi Arabia is currently the exception in that there is no formal agency authorisation procedure for clinical trials although this is expected to be implemented under the current regulatory reform and establishment of the Saudi FDA.

When asked whether ethics review procedures were a rate-limiting factor in obtaining CT approval, companies indicated that sequential processing, especially in Brazil and Malaysia, resulted in delays.

CT Review models

In countries with long-established Clinical Trial approval procedures, three models have evolved: A register of clinical trials where details are provided to the authority but specific authorisation is not required; An authorisation procedure where a CT application must be granted before the trial can commence; and a Notification/exemption procedure where an application must be submitted but trials can commence if objections are not raised within a specified time period.

In practice, in the Emerging Market countries studied, the notification/exemption option is not used and all countries except Saudi Arabia (see above) operate a clinical trial approval procedure.

Data requirements: All agencies require trials to be conducted in accordance with GCP and, as would be expected, the application data includes the Clinical Trial Protocol and Investigator's Brochure. All except Brazil have issued guidelines for sponsors on the application process and summaries of the supporting scientific data are accepted, except in China and India where full data are required.

Process map and timelines: The outline model for the stages in the review that is shown in the slide is generally applicable to most of the countries, the main differences being in the type of scientific assessment and whether applications are referred to an expert committee.

Most agencies use internal assessors to review CT applications, Egypt being the only country to use only external assessors. Only five of the 12 agencies studied review applications without involving an expert committee but several countries (e.g., Argentina, South Korea, Indonesia) only refer applications to their committees if there is a specific problem.

The general 'process map' indicates points at which review 'milestones' and time intervals could be logged but, in practice, data are only available, for the majority of countries, for the overall approval times. In some case (Argentina, South Africa, China, South Korea and Taiwan) separate targets were reported for the scientific assessment. The overall approval time targets ranged from 14 calendar days in Indonesia to 238 days in China. Some agencies, e.g., in Brazil, and India, make a distinction between trials that are part of a multinational programme and local registration trials and process the former more rapidly.

Questions to sponsors

The way in which questions are sent to sponsors can have an impact of the speed of response and the overall processing time. Most agencies batch the questions at the end of the assessment but South Africa asks questions as they arise and Taiwan aims to send questions 7-10 days into the assessment. In Mexico, regulations allow only one opportunity to ask questions and in Indonesia there is currently no mechanism to raise questions as detailed assessments are undertaken primarily by the Ethics Board.

The time allowed for responses is also very variable ranging from 7 days in South Africa to 60 days in Argentina.

Industry perceptions: Factors affecting effectiveness and efficiency

In the industry survey, companies were asked for their views on the factors that assist and impede the clinical trial application process in the Emerging Markets. Among the many and diverse comments were certain common themes:

Ethics Committee Approval: The timing in relation to the agency review, the advantages of parallel processing and the extent to which prior ethical approval, as part of multinational trials, was taken into account;

Access to agency staff: The willingness of authorities to cooperate and their availability to companies;

Guidance documents: The availability of information on requirements and procedures;

Resources: Whether the clinical trial review process was adequately funded with appropriate staffing etc;

Data requirements that are appropriate to the stage of development and the technical competence of the staff;

Timelines: The need for relatively short and predictable timelines, especially when clinical trials are being carried out as part of the global development of a new medicinal product.

GLOBAL CLINICAL TRIALS

A view from industry on the incentives, barriers and timings to be considered when undertaking clinical trial programmes outside the ICH regions was presented by **Dr Alasdair Davidson** on behalf of **Dr Paul Huckle, Senior Vice President, US Regulatory Affairs, GlaxoSmithKline, USA**, who was unable to attend.

Global clinical development addresses a global population, in which 80% of the people live outside the ICH region and in which patterns of disease (e.g., metabolic and cardiovascular) are becoming more similar to those in the 'West'. Global development programmes are facilitated by the rapid establishment of state-of-the-art 'centres of excellence' with a level of expertise that meets industry and regulatory requirements for adherence to GCP standards. The wider population in the new

markets helps to expedite patient recruitment, especially for drugs with a very narrow target population and it also provides access to 'drug naïve' patients. A properly designed global clinical programme should address questions of ethnic sensitivity and obviate the need for special studies (e.g. bridging studies).

Trials cannot, of course, be carried out in too wide a range of centres in case quality is compromised. As always, patient and/or volunteer safety is paramount.

Global development, by definition, must be parallel and therefore depends on supportive regulatory systems. Regulatory requirements must not be rate-limiting to the recruitment of patients and timelines must be defined and predictable in order to allow companies to plan a global strategy. One element of this is that the ethics approval procedure must be efficient and run in parallel, or not hold up, the Clinical Trial approval process.

The documentation required for the application must be appropriate to the stage of development. China was cited as an example where requirements for 'NDA-level' data in order to carry out even early stage trials, excludes the country from integration into global development programmes and, inevitably, delays patient access to new medicines. Countries participating in global programmes must also have mechanisms to manage change and allow data to be updated as the trial progresses.

The perceived incentives and barriers to global expansion of clinical development are outlined in the table.

Incentives and Potential Barriers	
Incentives	Barriers
Opportunity for local R&D investment in clinical capabilities (both within companies and externally)	Lack of access to Authorities for scientific advice or discussion
Acceptance of data in countries with similar ethnic population	Limited availability, visibility and scope of regulatory requirements
Possibility for earlier filing of a marketing application in countries where the clinical programme has taken place	Long/unpredictable approval times for CT applications
Access to volunteers and patients at the earliest opportunity	Limited acceptability of data generated in another territory
– e.g. ability to undertake first time in human studies in parallel across the world	

Access to scientific advice is an incentive to include a country in global clinical development especially if the advice can be regarded as 'binding'. Such advice can ensure that programmes are in alignment not only with regulatory needs but also those of local health care professionals and this should negate the need for extra work when the product is later presented as a marketing application.

It is clearly illogical for clinical trial approval that is part of global development to depend on prior marketing approval elsewhere (e.g., a CPP requirement). Timelines for clinical trial approval that exceed the 30-60 days achieved in the Western world may also preclude a country from inclusion in global development and the way in which Ethics Committees work is often a key factor.

In summary, to facilitate global drug development, regulators need to provide a clearly defined regulatory procedure, an efficient ethics approval procedure that runs in parallel with the regulatory procedure, clearly described regulatory requirements, application documentation that is appropriate to the phase of development, ensuring that the product is of quality and safe for use in humans, a defined mechanism for managing changes to the registered clinical trial information, and defined procedural timelines. Together, these elements will expedite patient access to innovative medicines.

CT AUTHORISATION AT NATIONAL LEVEL

The presentation on issues in global clinical development was followed by a panel discussion introduced by a presentation on the situation in Brazil and brief updates by the previous speakers from India, and Taiwan.

BRAZIL

Dr Jorge Samaha, *Coordinator, Clinical Trial Section, National Agency for Sanitary Surveillance (ANVISA)*, briefly summarised the history of his agency and discussed the way in which clinical trial applications are processed in Brazil.

Human medicines have been regulated in Brazil since 1976 but the control of clinical trials first started in 1988. **ANVISA** was created in 1999 with administrative and financial independence from the Health Ministry and the current regulations on Clinical trials were adopted in 2004. The regulations cover all clinical trials carried out on Brazilian territory and the import of non-licensed experimental drugs. CEPEC/GPBEN is the Portuguese acronym for Clinical Trials Coordination in the Office of New Drugs at ANVISA which reviews clinical trial protocols and runs the Programs on Expanded Access and Compassionate Use.

The current legislation is under discussion and future revisions are expected to improve the adverse reaction reporting system NOTIVISA, bring in definitive regulation of CROs and implements GCP inspections in accordance with PAHO guidelines.

The **National Health Council** (CNS) also has a role in the authorisation of clinical trials and focuses on ethical and social issues. Applications need both a scientific review by ANVISA and an ethical review by CNS but the industry can chose whether to follow a sequential or parallel path to obtain clearance.

The benefits of the two-route system include improved subject safety, review by two different institutions with different points of view of the same issue, and increased social control and accountability. Disadvantages include longer approval times, different definitions of clinical trials by the different parties, increased bureaucracy, and the need for a good interaction between the two institutions (which is often difficult in a heavily bureaucratic environment).

Clinical trials in Brazil have increased at rates exceeding growth in gross domestic product in 2005, 2006, and 2007. The work of CEPEC has resulted in better pre-marketing data on the Brazilian population and has contributed to the growing international credibility of the quality of data from Brazil. A recent publication⁹ ranked Brazil as the third most attractive international destination for outsourcing clinical trials (behind China and India).

Continuing challenges include shortening regulatory approval times, review of the regulations, establishing better regulatory landmarks for clinical trials, accommodating new technologies (e.g., therapeutic vaccines), improving information technology, and harmonising processes with other regulatory authorities (e.g., recognition of GCP inspections).

⁹ Arrowhead Publishers: Outsourcing Clinical Trials - A Global Analytical Guide and Comparative Analysis of International Destinations, with Location Attractiveness Index

INDIA

Dr Eswara Reddy, Office of Deputy Drugs Controller (India), CDSCO

The Drug and Cosmetics Act and Rules cover new drugs for clinical trials or for marketing and the regulation of clinical trials in India falls within the remit of the Central Drugs Control Organization (CDSCO). Investigational new drug applications and global clinical trial applications fall within the responsibility of the New Drugs Division and there is an IND Committee to which applications may be referred.

Clinical trials fall into two types: Global and Local. Global applications that are made as part of an international clinical programme are further subdivided:

- **Category A** where the trial protocol has been approved by an authority on the list of 'recognised' agencies and the timeline for approval is within 2-4 weeks;
- **Category B** other international trials where the timeline is 8 to 12 weeks.

The maximum approval time for all trials is 6 months.

For drugs discovered in India, local trials are conducted in India from Phase I. For drugs discovered elsewhere and destined for the Indian market, Phase I and II data must be submitted, and, depending on the type of drug, these studies may need to be repeated in India. In all cases, Phase III trials conducted in India are required for the marketing application.

Trials must be conducted in accordance with the requirements of GCP and also Indian Council for Medical Research (ICMR) guidelines, the Declaration of Helsinki and the CIOMS 'Ethical Guidelines for Biomedical Research on Human Subjects'. Other requirements include compliance with guidelines for writing SOPs for clinical trials, Good Laboratory Practices, the National Pharmacovigilance program, and bioequivalence and bioavailability guidelines.

As a location for carrying out clinical trials as part of global development, India offers the advantages of innovative scientific manpower, a cost-effective environment with low R&D costs, the strength of national laboratories, low cost chemical synthesis, state-of-the-art hospitals, a heterogeneous population, and a transparent judiciary. In addition India has recently implemented laws for intellectual property protection

There are, however, challenges to be met and these include ensuring that there is not a public perception that the Indian population are being used as 'guinea pigs' in the global development of medicines. Strict implementation of guidelines is important and new legislation is planned to bring the recognition and approval of ethics committee within the remit of ICMR and also to require the authorisation of clinical trial site. A remaining challenge is to set up a registry of clinical trials.

TAIWAN

Dr Herng-Der Chern, Executive Director, Center for Drug Evaluation, Taiwan, offered additional comments on the establishment of the Institutional Review Board (IRB) system in Taiwan.

Ten years ago there was a very conservative approach to clinical trials in Taiwan and such trials could only be performed in about a dozen medical centres. With the increasing globalisation of clinical development and use of multicentre trials, Dr Chern took the lead in establishing a Joint Institutional Review Board (IRB) among five leading medical centres to improve procedures for conducting trials in Taiwan. The government also implemented GCP and GCP inspections as well as establishing regional teaching hospitals. The environment for clinical trials has therefore matured over the years.

The fees charged for Joint IRB revenues has raised sufficient revenue for the establishment of a teaching foundation and an accreditation system for clinical trial centres that meets international standards and requirements. Eight medical centres have been accredited to date, by FERCAP¹⁰.

¹⁰ The Forum for Ethical Review Committees in Asia and the Western Pacific Region www.fercap-sidcer.org

The current situation is that there are now 133 hospitals that can conduct clinical trials in Taiwan. The Joint IRB can approve studies for 94 of these hospitals although companies may choose to apply to individual IRBs. The joint IRB concept has also been widely accepted elsewhere in Asia (e.g., Singapore, South Korea, Japan).

Three years ago, the government carried out an IRB audit and this has been followed by requirements for inspections. In the past 10 years, every trial in Taiwan has had a GCP inspection for one of the test sites and IRB inspections are now being carried out. A further development that is planned is the establishment of an IRB association in Taiwan.

It was suggested that other countries wishing to become part of global clinical trial programmes should focus on improving their arrangements for ethical review of clinical trials through IRBs.

POINTS FROM THE PANEL DISCUSSION

- **Taiwan joint IRB:** Herng-Der Chern clarified that in Taiwan, 90% of clinical trials are now reviewed by the Joint IRB; the other IRBs have neither the resources nor the expertise for this. The workload is large but the IRB meets every 2 weeks and the expert who is consulted must have a review completed within 1 week. If one expert cannot accommodate the task, when invited, another is sought immediately.
- **Latin America:** In Argentina, 1 in 3 clinical trial centres are now inspected, whereas 10 years ago, with an inspectorate of two, only 1 in 10 centres were inspected. The FDA has helped with training. With 400 ongoing clinical trials at any one time, one of the major challenges is managing the workload of the ethics committees.
- **Indian clinical Trials registry:** Dr Reddy clarified that India's registry of clinical trials is only in the preliminary stage and it is too early to be specific about the content and scope. A key question is deciding on the body that should maintain the registry. Procedural guidelines are being drafted.
- **Clinical trial material:** In response to a question on the source of clinical trial material in India, Dr Reddy explained that the products need not be manufactured in India, but may be imported from the parent company or other source. The company must, however, first obtain an import licence and apply for approval of the clinical trial.
- **EU Focus:** In a brief update on the situation in the EU it was pointed out that, under the Clinical Trial Directive, the authorisation of clinical trials remains the responsibility of individual Member States. Trials are not approved by the EMEA but the agency is responsible for issuing guidelines and giving Scientific Advice which would apply to trials conducted within or outside the EU.

Furthermore, Article 58 of Regulation (EC) No 726 2004 allows the EMEA, in the context of collaboration with WHO, to adopt opinions for medicinal products intended exclusively for markets outside the EU. This has involved inspections for compliance with GCP requirements for trials conducted in non-EU countries. These have been carried out in collaboration with WHO and with the local regulatory agency.

With regard to ethical review committees this is also outside the remit of the EMEA but a recent EU regulation on advanced therapies requires the presence of two ethics experts on the relevant advisory committees. This is an example of the interaction that is being established between scientific and ethical aspects of the review process.

ANNEX 1: RÉSUMÉ OF THE MAIN CONCLUSIONS AND RECOMMENDATIONS FROM THE WORKSHOP

TOPIC A: Models for Review Procedures and Types of Scientific Assessment

A1 Types of assessment

It was agreed that **multiple reviews by different authorities** of the core ('safety, quality and efficacy') scientific evidence for a new drug substance is not a good use of limited agency resources. By recognising the basic scientific review by at least two reference agencies, regulatory resources can be focused on the benefit-risk assessment of the finished product and its labelling, for the local market and on such activities as pharmacovigilance.

A2. An 'ideal' review process map

A common model or 'review map' for the sequence in which the different steps in a review are carried out is not a current priority. The focus should be on improving current systems rather than pressing for immediate, radical changes such as parallel rather than sequential review processes.

A3. Benefit Risk Assessment

Benefits would arise from **harmonisation of the criteria** for the benefit-risk assessment of new products, and may be feasible at a regional level but this is **not** a realistic international goal for the foreseeable future as such assessments remain subjective and are influenced by differences in health care systems, clinical practices and other cultural and historical differences.

TOPIC B: Evidence of authorisation by other Agencies

B1. The Certificate of a Pharmaceutical Product (CPP)

The CPP, issued in accordance with the *WHO Certification scheme on the quality of pharmaceutical products moving in international commerce* still has a recognised role in the global registration of medicines but radical changes to its format and scope are recommended.

- Acceptance of an **electronic CPP** and less reliance on original paper documentation is urgently needed to reflect the current technological environment;
- There should be a **separation of the role of the CPP** as a GMP certificate and as evidence of authorisation in the issuing country;
- A requirement for **marketing in the issuing country** should be removed from the CPP.

It was further recommended that the WHO ICDRA meetings and the ICH Global Cooperation Group should have a role in discussions to rationalise and update the use of the CPP and the Scheme in general.

B2 Alternatives to the CPP as evidence of registration

The type of evidence that is required about registration by other agencies should be more flexible and agencies that have the capability to carry out a full assessment should take steps to eliminate rigid CPP requirements from their review procedures. Information on existing authorisations that is posted on the Internet websites for the major agencies is a reliable substitute for a CPP in terms of accepting applications for review and validating the status of the product.

Where national regulations preclude such flexibility the agencies should initiate action and give their support to bring about local legislative change.

Topic C: Exchange of assessment reports

C1. Better use of reference agency reports

The reports published by the major agencies (e.g., the EMEA EPARs and the US FDA Summary Reports) are a valuable resource for other agencies but do not (and are not intended to) provide the detail of information needed by other agencies carrying out a detailed review of the same product. Where such detail is needed the agencies should work under confidentiality agreements and exchange full assessment reports, with the consent of the company concerned.

C2. Regional exchange schemes

It was agreed that the exchange of assessment reports between regulatory authorities in the same region (e.g., ASEAN members) would be a valuable step towards building mutual confidence between agencies and increasing harmonisation. It would not, however, be a *substitute* for receiving assessment reports from the reference agencies which first assessed the new medicines under review.

B2. The need for a common assessment template

It was recommended that the CMR International Institute should include, in its future work programme, a study of similarities and differences in the clinical sections of the assessment templates from a number of different agencies. It was agreed, however, that it was premature and over-ambitious to consider a project for internationally harmonised assessment template for new medicines, at this stage.

Topic D: Building Quality into the Review Process

D1. Quality standards and objectives

All agencies can improve the quality of their working practices but the standards set for building quality into the review should be realistic and '**fit for purpose**'. Targets need to be realistic and not set so high that they impede efficiency.

D2. Transparency

Building transparency into the review process drives improvements in the system to the ultimate benefit of the public and patient. Transparency requires political will as resources are needed but the investment has very positive benefits.

Topic E: Improving the Quality of Review Processes

E1. Project Management

Sound Project Management fundamental to improving and monitoring the quality of the review process. Two elements were identified as being of particular benefit:

- Providing a single point of contact within the agency with whom the company can communicate;
- Establishing a procedure for resolving contentious issues during the review by bringing together internal reviewers, the sponsor and, as appropriate, external advisors in order to avoid an impasse and subsequent appeal process.

E2. Feedback

It was recommended that all agencies should introduce mechanisms, no matter how rudimentary, of exchanging views and feedback with companies after the assessment of a major application for a new medicine.

E3. Tracking and monitoring systems

Good application tracking systems and effective project management are complimentary and inter-dependent. It was recommended that agencies with the facilities to monitor timelines and provide feedback should publish summaries of their findings and share these with industry and other interested observers, on an annual basis as part of the learning process.

ANNEX 2: BACKGROUND TO THE ROUND TABLE DISCUSSIONS

TOPIC A: Models for Review Procedures and Types of Scientific Assessment

The Study on regulatory procedures in Emerging Markets carried out by the CMR International Institute for Regulatory Science in 2006-2007 collected data on both the Regulatory Process, represented as a **Process Map** and the degree of detail of the Scientific Review categorised as the **Type of Assessment**.

An overview of these two aspects of the study was given in the presentation by Dr Neil McAuslane, CMR International Institute, in Session 1 of the Workshop: *Assessment models and process maps: A cross comparison between regulatory agencies*

Process Maps

The basic process map that is common to almost all agencies in both ICH-affiliated regions and the Emerging Markets consists of the following elements:

Validation → Scientific Assessment → Questions to Sponsor → Final Report → Approval Procedure

Some of the most noticeable differences that were found among agencies were in the procedures and the sequence for referring the application to outside experts or committees. Other differences were found in the timing of questions to the sponsor and in whether the different sections of the application (safety, quality and efficacy) were assessed in parallel or in sequence.

Types of Assessment

At the first Institute Workshop on the Emerging Markets, March 2006 (*Reference 1, inside front cover*), there was a discussion of the different ways in which agencies approach the scientific assessment of NAS applications and the extent to which they carry out a detailed examination of the data or rely on the work and opinions of trusted 'reference' agencies. A recommendation from the workshop was that:

'All parties would benefit from a much greater openness in accepting that most agencies do not have the resources and skills to carry out a full review of new active substance (NAS) applications and that there should be greater clarity in defining the review process that is actually followed.'

Based on this recommendation the Institute's Emerging Market study included the following classification of the review models and asked agencies which best described their own policies and procedures:

Data Assessment Type 1 ('Verification' Assessment)

This model avoids duplicating the assessment of a new product that is identical to one which has been approved elsewhere. The elements are:

- Recognition of an authorisation by one or more 'reference' or 'benchmark' agencies
- A 'verification' process to validate the status of the product and ensure that the product for local marketing conforms to the authorised product

Data Assessment Type 2 ('Abridged' Assessment)

This model also conserves resources by not re-assessing the full scientific supporting data but focuses on aspects that must be evaluated specifically for the local environment.

- It is a pre-requisite that the product has been registered by a 'reference' or 'benchmark' agency
- An 'abridged assessment' is carried out in relation to the use of the product under local conditions (e.g., focusing on aspects of quality such as stability and on a benefit-risk assessment for the local medical practice/culture and patterns of disease)

Data Assessment Type 3 (Full assessment)

In this model the agency has suitable resources, including access to appropriate internal and external experts, to carry out a 'full' review and evaluation of the supporting scientific data.

- A full, independent review of quality, pre-clinical (safety) and clinical (efficacy) data is carried out;
- Information on registrations elsewhere (if any) is taken into consideration but is not a pre-requisite to filing or for authorisation*.

*In practice, prior authorisation was a legal requirement in some countries, before local authorisation could be finalised, but filing the application and the review was not delayed.

Annex 2: Background to the Round Table Discussions

TOPIC B: EVIDENCE OF PRIOR AUTHORISATION IN THE REVIEW PROCEDURE

One of the routine pieces of information required whenever and wherever an application is made to market a new product is the product's regulatory status in other countries. Agencies that carry out a full independent review may not, however, require prior-authorisation elsewhere as a condition for granting an authorisation, and this is the case in the ICH affiliated countries.

For many authorities, however, there are requirements in the regulatory legislation stipulating that there must be evidence of prior authorisation by an agency with a recognised regulatory process (often known as a 'reference agency') before determining an application. Most often this takes the form of a **Certificate of Pharmaceutical Product** (CPP) as specified under the WHO Certification Scheme for the Quality of Products moving in International Commerce

Evidence of the regulatory status of a product can, however, take the form of:

- **A copy of the letter of authorisation** and appropriate accompanying documentation (e.g., summary of Product Characteristics in the EU) from the agency that has issued the authorisation;
- **Information on the official website** of the agency that issued the authorisation.

The CPP

The previous Institute Workshop on the Emerging Markets concluded that that:

'The principles and objectives of the WHO Certification Scheme, as a means of providing assurances on the regulatory status of products, remain valid but that guidance on the practical application of the Scheme needs to be updated. Lack of flexibility in requirements and a pre-occupation with the exchange of original paper documentation, in the electronic age of the 21st century, can be a significant impediment to the efficient and timely registration of new medicines'.

One of the hurdles when moving towards greater flexibility, however, is that the WHO has been so successful in the implementation of the Scheme that requirements for a CPP have been written specifically into national legislation in many countries. This limits the extent to which agencies can accept alternative evidence.

Copy of the authorisation from another agency

Some agencies in the CMR International Institute Study have indicated that they are prepared to accept a copy of a letter of authorisation from another agency as evidence that the product has been duly approved. In some cases this is only a 'holding' measure to allow an application to be submitted before the CPP is finalised but there are cases where this is the only evidence required.

Information available on the Internet

The regulatory agencies in the ICH-affiliated regions and many other authorities provide information on the regulatory status of medicines via their official websites. Web-based information, from reputable and trusted sites is being used increasingly as a source of information on many subjects but safeguards are, of course, needed to ensure the authenticity of the sites that are referenced.

Note on CPPs issued by the US FDA

Companies have been concerned about the FDA policy of issuing a CPP only for products that are exported from the USA. This has resulted in a situation where a product authorised for sale in the US, but manufactured elsewhere, is not eligible for FDA certification. The FDA position is that it has no jurisdiction to provide a certificate for a product that is exported from a non-US manufacturer to another country

FDA Pilot Scheme: At the Workshop an update was provided on the pilot scheme that FDA is operating under which it will provide certificates for products approved by FDA but not exported from the US when a CPP is not available from the country of manufacture. Strict conditions and safeguards on manufacturing conditions and compliance with GMP apply.

*ICH-affiliated regions refers to the three parties to ICH (USA, EU and Japan) and to those countries that are either formal Observers to the ICH process or have formally undertaken to adopt ICH guidelines (Canada, Switzerland, Australia, individual EU countries and the other EFTA countries, Iceland, Lichtenstein and Norway)

Annex 2: Background to the Round Table Discussions

TOPIC C: EXCHANGE OF SCIENTIFIC ASSESSMENT REPORTS

At the March 2006 Institute Workshop on the Emerging Markets it was recommended that:

'Agencies in the Emerging Markets should be encouraged to enter into formal agreements with their 'reference' agencies for the exchange of scientific evaluation reports, under suitable confidentiality agreements'.

Reference is often made to the Pharmaceutical Evaluation Report (PER) Scheme (abandoned in 2001) under which EFTA coordinated the preparation and exchange of assessment reports among participating agencies. The publication of detailed reports by the EMEA, in the form of European Pharmaceutical Assessment Reports (EPARs) was one of the major factors in EU countries withdrawing from the scheme.

Although there is unlikely to be support for reviving the PER Scheme, in the same form, among the ICH-affiliated agencies, there have been discussions of regional schemes, among agencies, for the exchange of evaluation reports, for example among the leading agencies in the Asia-Pacific Region.

Value of assessment reports from the Internet

The March 2006 Workshop on the Emerging Markets included a discussion of the value of the assessment reports that are published and made publicly available by EMEA as *European Pharmaceutical Assessment Reports* (EPARs)¹ and by the US FDA as *Summary Reviews*². Whilst the usefulness of these was recognised it was felt that they did not include the level of detail that would be required by regulatory agencies looking for an exchange of assessment reports. It was agreed, however, that the evaluation reports in an exchange scheme would not be expected to include details of, for example, the questions put to the company during the review process.

Workshop on Global Drug Development: Asia's role and contribution

When the CMR International Institute Workshop held in Japan in October 2006 the possibilities for cooperation between agencies in the Asia-Pacific region were raised and the report includes the following points from the Syndicate discussions:

"There would be value in building on existing informal/formal cooperation mechanisms available in the Asia-Pacific region and establishing an initial list of priorities for reducing barriers to early registration:

- There was recognition of the extensive bilateral arrangements already in place, particularly between the Japanese MHLW/PDMA and, for example, Taiwan, South Korea and Singapore.*

Networking would be facilitated by pairing between agencies and the establishment of a forum that include industry and agencies from the Western world as invited contributors"

The Workshop also discussed the feasibility of coordinated parallel reviews between one or more designated Reference Agencies in the Asia-Pacific Region and the EMEA/FDA. Other agencies participating in the Scheme would agree to 'recognise', in principle, the review by the consortium of agencies although it was recognised that the final conditions of authorisation may not be fully harmonised in all cases due to national considerations.

¹ EPARs are published on the EMEA website www.emea.eu.int

² "Drugs@FDA": Drug approval letters, label and review packages .Available from the CDER website: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Annex 2: Background to the Round Table Discussions

TOPIC D: BUILDING QUALITY INTO THE REVIEW PROCESS

Background

The Study on regulatory procedures in Emerging Markets carried out by the CMR International Institute for Regulatory Science in 2006-2007 included a section asking authorities about the measures that had adopted or were developing to improve and achieve higher quality standards and to meet the expectations of industry and the general public.

An overview of the outcome of this part of the study was given in Session 3 of the Workshop, in the CMR Institute presentation by Professor Stuart Walker: *Quality measures: A comparative view*.

In the study, agencies were asked about:

- Their internal quality policy defined as '*Overall intentions and direction of the organisation related to quality, as formally expressed by top management*'
- Good Review Practices defined as '*A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports*'
- Transparency of the review process defined as '*The ability and willingness of the agency to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry*'.
- Peer Review defined as '*an additional evaluation of the original assessment that is carried out by an independent person or Committee*'
- Standard Operating Procedures (SOPs) and assessment templates for written reports on scientific reviews
- Guidelines for industry and pre-application scientific advice offered to applicants
- Training and continuing education of agency staff as an element of quality

Institute Workshop on Quality of Review

In December 2004 the CMR International Institute held a Workshop on *Building Quality into Regulatory Dossiers and the Review Process*. On the subject of **Quality Reviews** the meeting made the following observations:

A quality review results in general satisfaction, on the part of both sponsor and agency, with the way in which the review procedures have been conducted and the outcome of the application process. The key elements are:

Assessments that are:

- Carried out in depth taking account of all the salient data and information
- Evidence-based with respect to the recommendation on the outcome
- Reported in sufficient detail to allow peer review
- Consistent within the different sections of the application
- Consistent between applications for similar products

Assessors that are:

- Consistent in approach and attitude to sponsors
- Creative, analytical and innovative in relation to novel products and concepts
- Focused on problem-solving

Annex 2: Background to the Round Table Discussions

TOPIC E: Project Management in the Review Process

Although the Institute Study on regulatory procedures in Emerging Markets in 2006-2007 included a section on *building quality into the regulatory process*, Project Management was primarily covered in terms of setting targets for review and approval times and the ability to track the progress of applications through the system.

In relation to the latter, Agencies were asked about their **tracking systems** and whether this enables:

- Tracing applications that are under review and identifying the stage in the process
- Signalling that target review dates have been exceeded
- Recording the terms of the authorisation once granted
- Archiving information on applications in a way that can be searched

Agencies were also asked about facilities to allow companies access to information on the progress of their applications

Feedback as part of project and quality management

Obtaining feedback from assessors, companies and other stakeholders is undoubtedly part of quality management but it can also be argued that improving the service provided to all interested parties is one of the objectives of good project management in the review process.

The Institute for Regulatory Science held a workshop in October 2004 on benchmarking regulatory procedures which focused on regulatory performance in the more advanced agencies. The meeting concluded that it is not enough to measure regulatory performance in terms of timelines and the speed of the review alone and that the quality of the process, from the construction of the dossier to the ultimate regulatory decision must also be monitored and added to the equation.

Institute 'Scorecards' project

The recommendations from the '*Benchmarking*' workshop and a subsequent workshop on '*Building quality into regulatory dossiers and the review process*', in December 2004 resulted in a major project being undertaken by the Institute to design and test a 'scorecard' system for obtaining feedback from both companies and agencies following the review of a major application.

- **Scorecard on the Industry:** This is designed to be completed by the **agency** and provides the company with views on the quality of the dossier and the way in which it interacted with the review process, with the objective of helping the sponsor understand the results of the review and learn from the outcome and update their internal procedures, if necessary.
- **Scorecard on the Agency:** This is completed by the **company** and gives views on the agency review in terms of the quality of service before submission (e.g., Scientific Advice) and during the review (e.g., interaction with the company, adherence to process guidelines etc.)

Apart from providing a harmonised feed-back system, one of the objectives of the Scorecard project is to encourage better working relationships between industry and regulatory agencies by providing a means for an open exchange of views on the conduct of a review.

ANNEX 3: NOTES ON THE INSTITUTE STUDY IN THE EMERGING MARKETS

Three presentations at the Workshop provided summary information from the CMR International Institute Study on the regulation of medicines in the Emerging Markets: Dr Neil McAuslane discussed assessment types and review models (Section 3, page 13), Professor Stuart Walker looked at the quality measures being implemented by agencies (Section 3 page 20) and Jennifer Collins presented the different ways in which Clinical Trial authorisations are handled (Section 3, page 37).

The Institute Study began in 2004 and the third phase had been completed at the time of the Workshop (see Figure 1). The initial 'fact finding' phase of the study covered the markets in some 30 countries but in the later stages the focus was on the 13 countries highlighted in Figure 2.

Figure 1

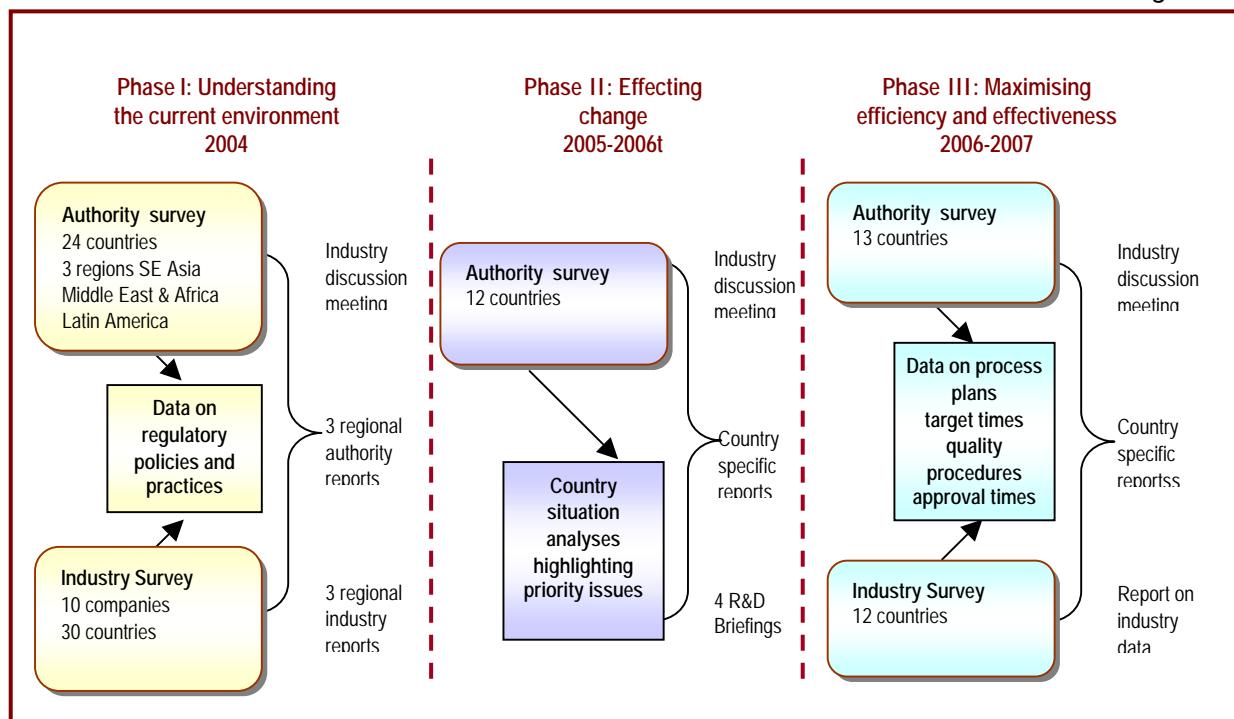


Figure 2

Latin America	Middle East and Africa	SE Asia and Western Pacific
Regional identification of emerging markets 	Argentina Bahrain Brazil Egypt Chile Colombia Costa Rica Mexico Venezuela Bahrain Egypt Jordan Kenya Kuwait Morocco Nigeria Oman Saudi Arabia South Africa Turkey UAE	China* Hong Kong India* Indonesia Malaysia Philippines Singapore South Korea Taiwan Thailand Vietnam

All the countries in the study are given in the table and those in bold print were followed up in the later Phases.

*Data on China and India was compiled from company sources and information in the public domain

Data collection: Phase 3 of the study

Data was collected from participating companies by using questionnaires. The information related mainly to timelines and metrics on applications to market new active substances (NASs) in the countries studied and on applications for major line extensions to authorised products. Where available, companies also provided information from their experience of applying for clinical trial authorisation in the target countries.

In the countries where data were also provided directly by the authorities (see figure 2) a questionnaire was used to define the scope of the study but information was primarily collected through face-to-face meetings with senior agency staff and follow-up discussion, where necessary.

The scope of the data collection is summarised in Figure 3 which also shows the three sections of information, as discussed by the CMR Institute speakers.

Figure 3

